Integrated Master in Bioengineering

Department of Chemical Engineering

Removal of 5-Fluorouracil from water by adsorption processes

Master's Thesis

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“Nada na vida deve ser temido, somente compreendido.
Agora é hora de compreender mais para temer menos.”

Marie Curie

Abstract

Cytostatic drugs are a class of pharmaceutical compounds that are increasingly used in cancer therapies. 5-Fluorouracil (5-FU) is one of the most commonly used cytostatic drugs worldwide. Cytostatic drugs and most of pharmaceuticals are not completely metabolized by human body, whereby they are excreted unchanged or only slightly transformed to the sewage system and consequently reach the environment. The concern about cytostatic anticancer drugs in the environment is increasing mainly due to their carcinogenic, mutagenic, teratogenic, genotoxic, and cytotoxic effects, even at low concentrations. Advanced oxidation processes (AOPs) are frequently used to remove compounds with a high chemical stability and/or low biodegradability, as 5-FU; however they are an expensive approach, when concentrations are very low. In this work, a new strategy to pre-concentrate 5-FU through adsorption is studied. Activated carbons, carbon blacks and zeolites were tested as adsorbent materials.

Zeolite materials tested demonstrated to be inefficient to remove 5-FU, even at extreme conditions (4000 mg/L of adsorbent), being discarded from this study. By contrary, activated carbons and carbon blacks presented good adsorption properties for 5-FU removal from water. Adsorption kinetics were better fitted by pseudo-second order model than by pseudo-first order. Under the conditions tested, BP2000 presented the fastest uptake of 5-FU, with a k_2 of 0.40 and 0.27 for 1 and 10 mg/L of 5-FU, respectively. The fast kinetic for both carbon blacks (BP2000 and Vulcan XC72) were in line with the higher volume of mesopores as compared to activated carbons. For BP2000 and Norit carbons, the agitation seemed not influence the kinetics of adsorption. However, it was observed a faster uptake of 5-FU from water, when small particles of both adsorbents were used. It was also verified that intraparticle diffusion seems to be the only step influencing adsorption of 5-FU on carbon materials. It was also noticed that there isn't an isotherm model which describes equilibrium data for all the carbon materials. While the adsorption of 5-FU on BP2000, Merck, Vulcan XC72 and Wittco is better described by Freundlich model, the adsorption on CECA is better fitted by Langmuir and Norit by Sips. It was noticed an increase of adsorption capacity with surface area. Since this relation is not described by a linear function, it is suggested that chemical surface nature may also influence the adsorption process.

Keywords: 5-fluorouracil, activated carbon, carbon black, adsorption, isotherms, kinetics

Resumo

Citostáticos são uma classe de compostos farmacêuticos que são cada vez mais utilizados em terapias de cancro. 5-fluorouracil (5-FU) é um dos citostáticos mais usados em todo o mundo. Citostáticos e a maioria dos fármacos não são completamente metabolizados pelo corpo humano, sendo excretados inalterados ou ligeiramente transformados para o sistema de esgotos, atingindo o meio ambiente. A preocupação com a presença de citostáticos no ambiente tem vindo a aumentar, principalmente devido aos seus efeitos cancerígenos, mutagénicos, teratogénicos, genotóxicos e citotóxicos, mesmo quando a sua presença é em baixas concentrações. Processos de oxidação avançada são frequentemente utilizados para remover compostos com uma alta estabilidade química e/ou baixa biodegradabilidade, como o 5-FU; no entanto, eles são uma abordagem dispendiosa, quando as concentrações são muito baixas. Neste trabalho, é estudada uma nova estratégia de pré-concentração do 5-FU através de adsorção. Os carvões activados, os negros de fumo e zeólitos foram testados como materiais adsorventes.

Os zeolitos testados demonstraram serem ineficazes na remoção de 5-FU, mesmo em condições extremas (4000 mg/L de adsorvente), sendo por isso descartados deste estudo. Pelo contrário, os carvões activados e negros de fumo apresentaram boas propriedades de adsorção para a remoção de 5-FU da água. As cinéticas de adsorção foram ajustadas de forma mais correcta pelo modelo de pseudo-segunda ordem do que pelo de pseudo-primeira ordem. Sob as condições testadas, BP2000 apresentou a mais rápida adsorção de 5-FU, com um k_2 de 0,40 e 0,27 para 1 e 10 mg/L de 5-FU, respectivamente. A rápida cinética para ambos os negros de fumo (BP2000 e Vulcan XC72) estava em linha com os maiores volumes de mesoporos, em comparação com carvões activados. Para os carvões BP2000 e Norit, a agitação parece não influenciar a cinética de adsorção. Porém, foi observado uma captação mais rápida de 5-FU da água, quando partículas mais pequenas de ambos os adsorventes são usadas. Foi também verificado que a difusão intraparticular parece ser o único passo a influenciar a adsorção de 5-FU em materiais de carbono. Foi observado que não existe um modelo de isotérmica que descreva os dados de equilíbrio para todos os materiais de carbono. Embora a adsorção de 5-FU em BP2000, Merck, Vulcan XC72 e Wittco seja melhor descrita pelo modelo de Freundlich, a adsorção do CECA é melhor ajustada pelo modelo de Langmuir e do Norit pelo Sips. Foi constatado um aumento da capacidade de adsorção com a área superficial; uma vez que esta relação não é descrita por uma função linear, sugere-se que a natureza química de superfície também possa funcionar como um factor condicionante da adsorção.

Palavras-chave: 5-fluorouracil, carvão activado, negros de fumo, adsorção, isotérmicas, cinéticas

Declaration

The author declares, under oath, that this work is original and that all non-original contributions were properly referenced.

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Nomenclature

Abbreviations

2D	Two-dimensional
5-FU	5-Fluorouracil
AOPs	Advanced oxidation processes
ATC	Anatomical Therapeutic Classification
BCF	Bioconcentration factor
BET	Brunauer-Emmett-Teller
CP	Cyclophosphamide
DHFU	Dihydrofluorouracil
dNTP	Deoxynucleotide
DOX	Doxorubicin
DPD	Dihydropyrimidine dehydrogenase
dUTP	Deoxyuridine triphosphate
FdUMP	Fluorodeoxyuridine monophosphate
FdUTP	Fluorodeoxyuridine triphosphate
FUTP	Fluorouridine triphosphate
GAC	Granular activated carbon
GO	Graphene oxide
HSDM	Homogeneous surface diffusion model
IF	Ifosfamide
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde
LOD	Limit of quantification
LOQ	Limit of quantification
MET	Methotrexate
MIP	Molecular imprinted polymer
MRI	Magnetic resonance imaging
MWCNT	Multiwalled carbon nanotubes
MSC	Model selection criterion
PAC	Powdered activated carbon
RSD	Relative standard deviation
TGA	Thermogravimetric analyzes
TS	Thymidylate synthetase
WWTP	Wastewater treatment plant

Notation

b	Temkin constant	J.g/(mg.mol)
C	Concentration of the adsorbate in the liquid phase	mg/L
C_0	Initial concentration of adsorbate in the liquid phase	mg/L
C_e	Equilibrium concentration of adsorbate on the solution	mg/L
I	Intraparticle diffusion constant	mg/g

k_1	kinetic constant of pseudo-first order	L/g/min
k_2	kinetic constant of pseudo-second order	L^2/g/min/mg
k_d	Intraparticle diffusion rate constant	mg/(g.$min^{1/2}$)
K_F	Freundlich constant	mg/g/(mg/L)$^{1/n}$
K_H	Henry's law constant	atm.m^3/mol
K_L	Langmuir adsorption equilibrium constant	L/mg
K_{OC}	Organic carbon partition coefficient	
K_{OW}	Octanol-water partition coefficient	
K_S	Sips constant	
K_T	Equilibrium binding constant	L/mg
L_0	Mean micropore width	nm
m	Number of experimental points	
n	Mass of adsorbate in the liquid phase	mg
n_F	Freundlich constant	
n_S	Sips constant	
p	Number of fitting parameter	
pKa	Dissociation constant	
pI	Isoelectric point	
q	Adsorbate concentration in the solid phase	mg/g
q_{calc}	Calculated adsorbate concentration in the solid phase	mg/g
q_e	Equilibrium concentration of adsorbate on the adsorbent	mg/g
q_L	Maximum monolayer capacity	mg/g
q_{meas}	Measured adsorbate concentration in the solid phase	mg/g
q_S	Maximum monolayer capacity	mg/g
R	Correlation coefficient	
R	Universal gas constant	J/K mol
S_{BET}	Apparent surface area	m^2/g
S_a	Standard deviation of intercept	
S_b	Standard deviation of slope	
$S_{y/x}$	Standard deviation of residuals	
T	Temperature	^{o}C or K
t	Time	min
V	Solution volume	L
V_{meso}	Mesopore volume	cm^3/g
V_{micro}	Micropore volume	cm^3/g
V_{Total}	Total volume	cm^3/g
W	Adsorbent mass	g

1 Introduction

1.1 Cytostatics

Cancer is currently the leading cause of death in the world, after heart and infectious diseases [1]. The most common cancer treatments are chemotherapy and radiation, both having several limitations and side effects [2]. The selection of therapy is dependent upon the cancer type (small cell or non-small cell), genetic characterization and development stage [3]. The number of patients treated by chemotherapy had increased in the last decades and is expected a growth on cancer incidence for the following years [4]. Cytostatic drugs are used in chemotherapy, among various classes of pharmaceutics, and a growth in their demand is expected in developed countries [5].

Cytostatic drugs are classified under Antineoplastic and Immunomodulating Agents by the Anatomical Therapeutic Classification (ATC) developed by the Wold Health Organization. ATC divides them according to the similar therapeutic action in five sub-groups: alkylating agents, antimetabolites, plant alkaloids and other natural products, cytotoxic antibiotics and related substances and other antineoplastic agents [6].

Cytostatics and most of pharmaceuticals are not completely metabolized by human body, whereby they are excreted unchanged or only slightly transformed to the sewage system [7]. The most used cytostatics have been 5-fluorouracil (5-FU), ifosfamide (IF), cyclophosphamide (CP), methotrexate (MET) and doxorubicin (DOX), being the levels found in the aquatic environment in the range of ng/L to µg/L [8]. These chemotherapy drugs don't recognize the difference between the cancerous cells and the normal cells, which is problematic, since cytostatics have potential carcinogenic, mutagenic, genotoxic, cytotoxic and teratogenic effects [9], even at low concentrations [7]. Their presence in wastewater effluents potentiate the spread of such compounds in the environment through water and soil/sediments contamination [10] and may cause consequences to both human and wildlife [11]. Hospitals and specialized cancer hospitals are frequently considered the main sources of cytostatics, due to the intensive anticancer medication of patients under treatment [10] and the uncontrollable release of such drugs through excretions [12]. In the present work, 5-FU was selected as a case study substance regarding the proposal of a suitable adsorption process to remove cytostatics from contaminated waters. According to the prescription data provided by *Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.* (INFARMED), 5-FU is one of the most used cytostatics in Europe.

1.2 5-Fluorouracil

Cytostatic 5-fluorouracil (5-FU) belongs to the class of antimetabolites [13] and is a pyrimidine analogue, which is widely applied in cancer treatment, especially colon, neck, head and ovary cancers [14]. It was introduced in 1957 for clinical use and remains one of the most effective chemotherapeutic agents [15] and also one of the most used [8].

Antimetabolite drugs act by inhibiting essential biosynthetic processes, or by being incorporated into macromolecules, such as DNA and RNA, inhibiting their normal function. The fluoropyrimidine 5-FU does both. It is converted intracellularly into several active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP) and fluorouridine triphosphate (FUTP). These active metabolites disrupt RNA synthesis and the action of thymidylate synthetase (TS) (Figure 1.1). TS is necessary for DNA replication and repair, which is interrupted by its inhibition. Also results in deoxynucleotide (dNTP) pool imbalances and increased levels of deoxyuridine triphosphate (dUTP), both of which cause DNA damage. More than 80% of administered 5-FU is normally catabolized primarily in the liver, where dihydropyrimidine dehydrogenase (DPD) is abundantly expressed, which converts 5-FU to dihydrofluorouracil (DHFU) and interferes with the antitumour efficacy of 5-FU [16].

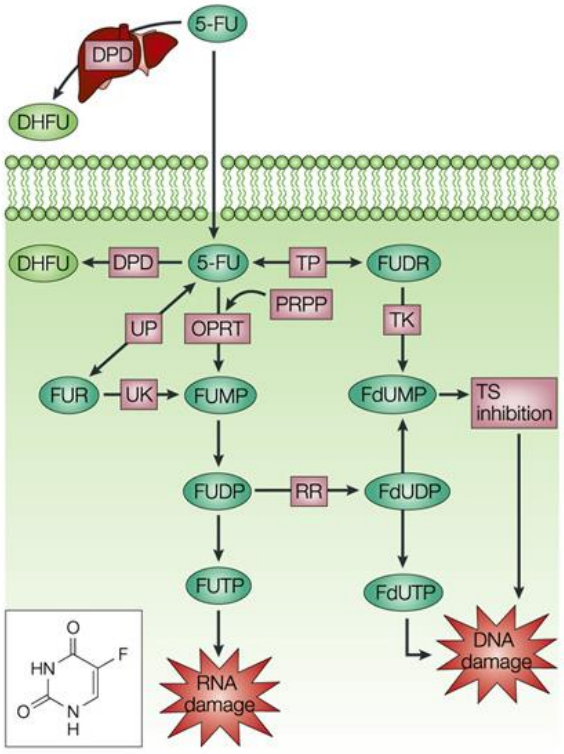


Figure 1.1. 5-FU metabolism [16].

Currently, 5-FU is mostly administered intravenously in either clinics or hospitals [17]. There is a dependence of the administrated dose with the schedule and the disease [18], being the dosages in the range of 200-1000 mg/m^2 body surface [19]. The concentration of the injected solution is 50 mg/mL [20]. For topical use, the application can be made by cream (20-50 mg/g) or solution (20-50 mg/mL) [21]. Approximately 2–35% of the administered drug is excreted unmetabolised via urine within 24 h [19].

The main physical-chemical properties of 5-FU are represented in Table 1.1. By the melting and boiling point is verified that 5-FU is a non-volatile compound, which is important in terms of security, when it is manipulated. It has a maximum UV radiation absorption among 265 and 266 nm, meaning that is poorly susceptible to direct photolysis by natural sunlight. The pKa of 8.02 puts 5-FU in weak acids group and corresponds also to its isoelectric point [22]. Thus, 5-FU molecule is predominately negatively-charged at pH values above 8, at pH 7.4 about 25% of 5-FU is ionized, being practically neutral at pH 6 or lower [23]. Figure 1.1 helps to visualize the net charge variation of 5-FU molecule with pH.

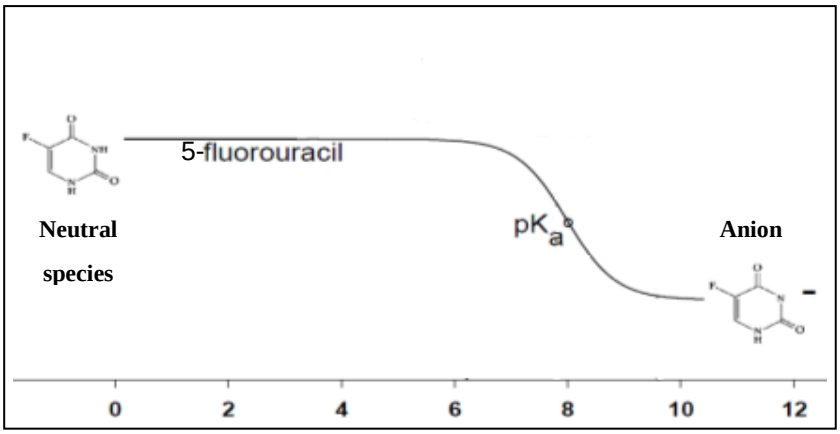


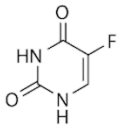
Figure 1.2. Changes in the ionization state of 5-FU molecule as a function of solution pH. Adapted from [50].

The extremely low vapour pressure (2.68×10^{-6} mmHg) and Henry's law constant (1.66×10^{-10} atm.m^3/mol) allows to conclude that 5-FU is mainly distributed in liquid and solid phases (e.g. activated sludge, biofilm, suspended solids, soil and sediments). The low octanol-water partition coefficient ($10^{-0,89}$) suggests that it has low adsorption to suspended solids in water, but high mobility in soil/sediments, due to its organic carbon partition coefficient (K_{oc} 8). 5-FU has a half-life of 39.6, 360, 720 and 3240 hours in air, water, soil and sediments, respectively [24]. This means that it is more persistent in sediments, followed by soil, water and air. Besides these results, water is the major problem, since it is the carrier medium to spread 5-FU in the environment.

The low BCF (3) indicates that it is unlikely that 5-FU will be accumulated in aquatic organisms. The biodegradability of 5-FU was intensively studied. No 5-FU biodegradation (initial concentrations ranging from 9 to 854 mg/L) was observed under different conditions [13]. Some opposite results were reported, but it may result from false negatives, caused by its cytotoxic effect on the degrading microorganisms [25] This effect may results from 5-FU structure formed by

halogenic atoms [17]. Therefore, it will be rather persistent in natural water bodies [10]. The high solubility of 5-FU in water also contributes to its accumulation in the aquatic environment.

Table 1.1. Physical-chemical properties of 5-FU [26] [27] [28] [24] [19] [29].

Compound identification (name and structure)	5-fluoro-1H-pyrimidine-2,4-dione 5-Fluorouracil 
Molecular formula	$C_4H_3FN_2O_2$
Molecular weight	130.077 g/mol
Volume	95.34 $Å^3$
Boiling and melting point[1]	Decomposes at 282-283 ^oC
Water solubility at 22 ^oC	1.11×10^4 mg/L
pKa	8.02
Vapor pressure	2.68×10^{-6} mmHg
K_{ow}	$10^{-0.89}$
K_{oc}	8
K_H	1.66×10^{-10} atm.m^3/mol
BCF	3
Half-lives	39.6 hr in air 360 hr in water 720 hr in soil 3240 hr in sediment
Excretion	2 – 35%
UV_{max}	265-266 nm

Notes: BCF – Bioconcentration factor; K_H – Henry's law constant; K_{OC} – organic carbon partition coefficient; K_{OW} – organic carbon partition coefficient; pKa – dissociation constant.
[1] Sublimes (0.1 mmHg) at 190-200 ^oC. When heated to decomposition it emits very toxic fumes of hydrogen fluoride and nitrogen oxide.

5-FU is worldwide produced and consumed, being released to the environment through various waste streams [17]. The concentrations of 5-FU in wastewaters vary from study to study, being some values compiled in Table 1.2. The highest measured 5-FU concentration was found in wastewater produced by oncological wards (150 µg/L). It is evident from these data that hospital wastewater contributes in great degree to the loads of these contaminants and that hospital effluents are the primary but not the only source of 5-FU in municipal wastewater and in the environment in general. Since 5-FU is hydrophilic and doesn't have the potential to be readily sorbed to the sludge, it is unlikely to be removed in wastewater treatment plants (WWTP) [17]; the data presented in Table 1.2 proves it.

Table 1.2. 5-FU occurrence in wastewaters.

Matrix	Concentration range (µg/L)	Reference
WWTP effluent	< 0.006 - 0.015	[30]
WWTP effluent	0.0083 – 0.01	[31]
Municipal wastewater	0.0047 – 0.014	[32]
Hospital wastewater	< 0.005 - 0.027	[30]
Hospital wastewater	< 0.027	[33]
Hospital wastewater	0.027 - 124	[17]
Hospital wastewater	0.035 – 0.092	[32]
Hospital wastewater (oncological ward)	4 - 150	[19]
Hospital wastewater (oncological ward)	20 - 122	[34]

A genotoxic study on eukaryotic yeast revealed that the minimal genotoxic concentration of 5-FU is 20 µg/L [30]. Teratogenic and carcinogenic effects have a concentration threshold of 0.005 to 0.05 µg/L [8] and 0.23 µg/L [35] respectively. Therefore, there is the risk of teratogenic, carcinogenic and genotoxic effect in specialized cancer hospital effluents, the risk of teratogenic and carcinogenic in hospital effluents and teratogenic effect in municipal and WWTP effluents. All these facts justify the purpose of this thesis and the urgency in finding effective processes to remove cytostatics from water.

1.3 5-FU removal processes

5-FU removal by conventional wastewater treatment is often incomplete and inefficient [36], as is proved by the data shown in Table 1.2. There are several tertiary treatment systems currently used at WWTP as microfiltration, ultrafiltration, reverse osmosis, sand filters, among others, although they seem not be effective in the removal of 5-FU as standalone processes [37].

On the other hand, advanced oxidation processes (AOPs) are frequently used to remove components with a high chemical stability and/or low biodegradability (e.g. 5-FU), producing a complete mineralization to CO_2, water, and inorganic compounds, or at least their transformation into more innocuous products. Moreover, AOPs represent interesting alternatives, since they can be employed in association with biological treatments for wastewater remediation, as a pre-treatment, increasing the biodegradability through partial oxidation, or as a post-treatment for the degradation of persistent compounds, being at the same time cost efficient and extremely viable from an economic perspective [38] [39].

AOPs can be classified either as homogeneous or heterogeneous. Homogeneous processes can be further subdivided into processes that use energy and processes that don't use it (Figure 1.3). Among these AOPs systems, they have in common the formation of ·OH species (hydroxyl

radicals), which are very reactive to organic molecules, but not selective. The oxidation reaction is following described [40] [41], when leading to complete mineralization:

$$AOPs \rightarrow \cdot OH + \ pollutant \rightarrow \ldots \rightarrow CO_2 + H_2O + inorganic\ ions \qquad \text{Eq. 1.1}$$

The treatment of pharmaceuticals, as 5-FU, in aqueous media by AOPs is likely to be an expensive approach, when concentrations are very low [42]. Thus, since none of the referred processes (including the biological) as standalone units allow an efficient removal of 5-FU, emerges the necessity to develop combined removal methodologies (e.g. adsorption + AOPs). The focus of this work will be the first step of this new approach: the concentration of effluent by adsorption to be posteriorly degraded by AOPs.

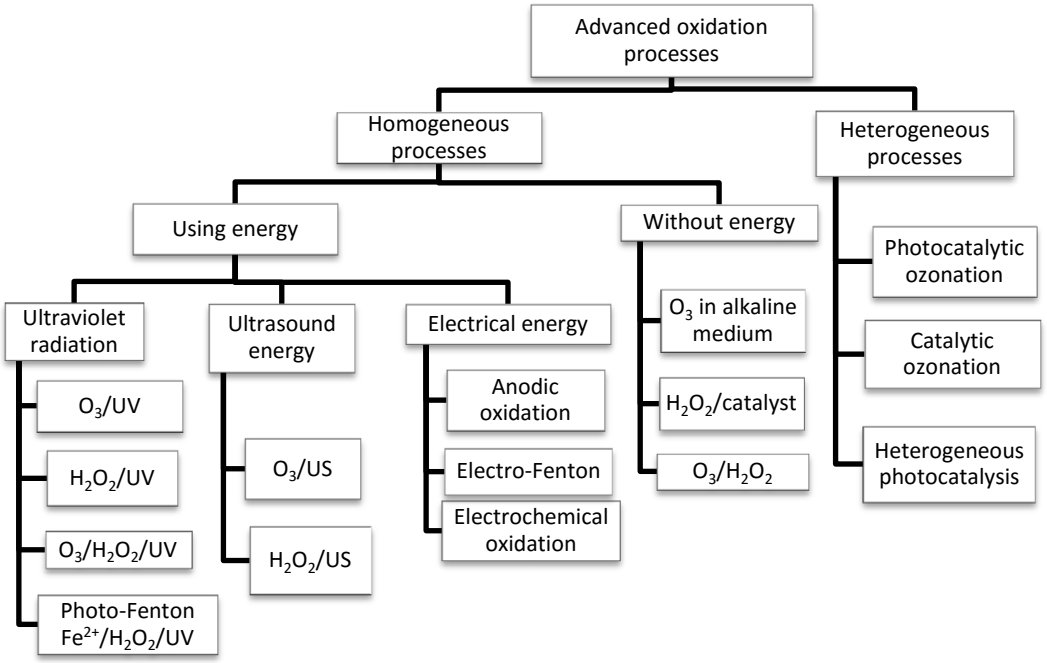


Figure 1.3. AOPs classification. Abbreviations used: O_3 - ozone; H_2O_2 - hydrogen peroxide; UV ultraviolet radiation; US - ultrasound energy; Fe^{2+} - ferrous ion [43].

1.4 Adsorption

Adsorption is a phase transfer process that is widely used in practice to remove substances from fluid phases (gases or liquids). It can be observed as a natural process in different environmental compartments. In water treatment, adsorption has been proved to be an efficient removal process for a multiplicity of solutes. Herein, the molecules are removed from the aqueous

solution by adsorption onto solid surfaces [44]. It is recognized as an efficient, promising and widely used approach for wastewater treatment; simple, economically viable, technically feasible and socially acceptable [45]. It is important to distinguish adsorption from absorption. While the first one is described as the enrichment of adsorbates (substance that is adsorbed) on the surface of an adsorbent (material where adsorption occurs), in absorption the enrichment is not only on its surface, but within the receiving phase. In natural systems, there are some complex materials where both situations can happen. In such cases, it is not easy to distinguish between adsorption and absorption, whereby the more general term used is sorption [44].

1.5 Types of adsorption – physical and chemical

In adsorption there are two main forces driving the overall process. The first one is related to the lyophobic character of the solute, in other words, the solubility of the solute in the adsorption solvent: the higher the interaction between the adsorbate and the solvent where it is present, the lower the adsorption of the adsorbate on the adsorbent and vice versa. The second driving force is the affinity of the adsorbate to the adsorbent. It can result from van der Waals attraction, generally termed physical adsorption, or from chemical interaction, usually named chemical adsorption. Physical adsorption is independent of the electronic properties of the adsorbent and adsorbate molecules. The adsorption is nonspecific and is reversible. Multiple layers may be formed and it is characterized by relatively low adsorption energy. Chemical adsorption involves an exchange of electrons between specific surface sites and solute molecules, a chemical bond is formed. The adsorption is very specific and is irreversible. Generally, only a single molecular layer can be chemically adsorbed.

These two forms of interaction between solute and adsorbent occur simultaneously in the adsorption process. The solute is less strongly attached to a specific site in physical adsorption compared to chemical adsorption. Therefore, physically adsorbed molecules are free to move within the interface. Besides the large range of binding energies (lower energies in physical adsorption and higher energies in chemical adsorption), it is generally very difficult to distinguish them [46].

1.6 Factors Influencing Adsorption

Adsorption is not a uniquely homogeneous process, but is rather dependent on various factors. Temperature, pH of solution, presence of competing compounds and agitation are some external factors affecting adsorption, while surface area, porosity, chemical surface and moisture content are some intrinsic properties of adsorbents with an important role, as well, in adsorption process. These factors will be briefly addressed below, focusing particularly solid-liquid systems.

1.6.1 Temperature

Adsorption has usually an exothermic nature, whereby is possible to conclude that decreasing the temperature will favor the uptake of the solute by the adsorbent under equilibrium conditions. Since low temperature processes are very expensive in large scale, this is a variable hard to regulate [47]. While exothermic adsorption is a constant reality in physical adsorption, endothermic chemical adsorption has been observed as well, being the increase of temperature favourable to the adsorption process from the thermodynamic (equilibrium) point of view [48]. Moreover, increasing the temperature increases the rate of diffusion of the solute through the liquid to the adsorption sites, which eventually leads to an increased adsorption rate [46]. Although, since adsorption involves specific relations between the adsorbent and the solute, the quantitative effects of temperature are not the same for all adsorbents and solutes [49].

1.6.2 pH of solution

Adsorption performance is strongly dependent on the solution pH, especially when ionizable compounds are being studied (e.g. 5-FU). It is necessary to play with the pH to ionize the adsorbent and adsorbate in such a way that adsorption is promoted. Since the 5-FU molecule is in its negative form for pH values higher than 8 (Figure 1.2), the adsorption may be favored for positively charged adsorbents at these pH conditions. On the other hand, it is necessary to take into account the interactions with the solvent; adsorption process could be compromised, due to the increase of adsorbate solubility at some pH values. The ideal pH can be achieved finding a middle term among these two behaviors [47] [50].

1.6.3 Competing compounds

In real water samples, the performance of adsorption processes will always be influenced by the presence of organic/inorganic species. In most cases, these species will compete with the adsorbate molecule for the adsorbent and naturally reduce its capacity towards the target analyte. The competition is less pronounced at high adsorbent doses than at low adsorbent doses, when the number of sorption sites is very limited [47]. The ability to selectively recognize a target molecule in a pool of similar molecules is essential to biological and chemical processes, which is achieved by molecular imprinted polymers (MIPs) [51].

1.6.4 Agitation

Agitation is a very important factor influencing the adsorption of organic compounds on solid adsorbents. Generally, the adsorption rate increases with an increase in the agitation speed [52], at

least up to point where turbulence is important enough, leading to negligible external mass transfer resistances. However too much agitation can lead to the destruction of the structure of the adsorbent and make the process inefficient. The kind of agitation can influence the kinetics of adsorption. For example, the use of mechanical and magnetic stirrers should be avoided because the contact of the adsorbent with the stirrer paddles or bars may cause particle size reduction [52].

1.6.5 Surface area

The extent of adsorption is generally considered to be proportional to the specific surface area. Therefore, it is expected that the greater the surface area of the adsorbent, the greater the mass of the solute adsorbed. Specific surface area (surface area per gram of adsorbent) is the proportion of total surface area that is available for adsorption. The surface area of an adsorbent depends on its structure; in general, the more finely divided and more porous adsorbents would be expected to yield more adsorption per unit weight of adsorbent. The surface can be characterized either as external (when it involves bulges or cavities with width greater than depth) or internal (when it involves pores and cavities that have depth greater than width) [46]. The specific surface area can be calculated by applying the Brunauer-Emmett-Teller (BET) equation to the isotherms generated during the adsorption process of e.g. nitrogen. The adsorption of N_2 at 77 K (or CO_2 at 273 K) are the most commonly used to produce these isotherms. The BET theory is based upon the assumption that the monolayer is located on surface sites of uniform adsorption energy and multilayer build-up via a process analogous to the condensation of the liquid adsorbate [53].

1.6.6 Porosity

Adsorption is a process dependent on the accessibility to the internal surface, being the pore structure a very important property for adsorbent materials. The adsorption capacity and the rate of adsorption are determined by the total number of pores and their shape and size [46]. According to IUPAC, porosity can be classified in three groups: micropores, when pores are not larger than 2 nm, mesopores with a width among 2 and 50 nm and macropores higher than 50 nm [54]. Porosity can be characterized by the specific surface area, pore volume and pore size distribution. In the case of macropores, surface area can be neglected. For mesopores, the three parameters previously mentioned are fundamental, since monolayers and multilayer adsorption takes place on its surface [55]. Both macro and mesopores play an essential role to transport molecules to the micropores, which contain most of the surface area [56]. For micropores, all atoms of the adsorbent can interact with the adsorbate species, whereby adsorption is a pore-filling process, where the pore volume is the main controlling parameter [55].

1.6.7 Chemical surface characteristics

The chemical surface characteristics of the adsorbent significantly contributes to the adsorption performance. Several elements as hydrogen, oxygen, nitrogen and sulfur, as well as inorganic mineral matter, may be present in adsorbent materials, particularly in carbon-based. All of these heteroatoms influence the properties of the carbons in many ways, but the greatest influence comes from the presence of oxygen [53]. The presence of oxygen groups, even in small quantities, will affect the surface properties such as surface acidity, polarity or hydrophobicity, and surface charge. Certain oxygen-containing surface functionalities such as chromene, ketone, and pyrone can contribute to the carbon basicity, while carboxylic acid or carboxylic anhydride, lactone, and phenolic hydroxyl, have been postulated as sources of surface acidity [57]. The several types of oxygen groups to be found on adsorbent surfaces, because of the electronegativity of the oxygen atoms, possess dipole moments and their presence has a marked effect on the shapes of adsorption isotherms of polar adsorbates [58]. They may also reduce the adsorption capacity, due to co-adsorption of water via hydrogen bonding [59]. The presence of oxygen increases the polarity of the adsorbent surface; therefore, the affinity to water is higher. The adsorbed water may block adsorbent pores and consequently restrict the access to hydrophobic regions on the adsorbent surface, the entrance of solutes in micropores and the interaction between the solute and adsorbent surface [60] [61].

1.6.8 Moisture

Adsorbents are considered moisture free content, if packaged in airtight containers. Otherwise, they will absorb moisture over time. In the case of activated carbon (focus of this thesis), it may adsorb as much as 25% to 30% moisture and still appear dry. For many purposes, the moisture content doesn't affect the adsorption capacity, but may restrict the entrance of some solutes in the pores, as explained before. To obtain the dry weight of adsorbent, a drying at 110 ^{o}C should be performed during 24 hours and then keeping the sample in a desiccator over a suitable dehydrating agent. However, there is the possibility of some adsorbents experience an appreciable loss of adsorptive power when dried [49].

1.7 Adsorption kinetics

Knowledge of adsorption kinetics is necessary to understand the mechanism and rate of adsorption and determine equilibrium time. In full-scale batch process, they are helpful for selecting optimum operating conditions [62]. Different adsorbents have different pore structures and different surface chemistries, therefore adsorption rates may be controlled by pore, surface or external film

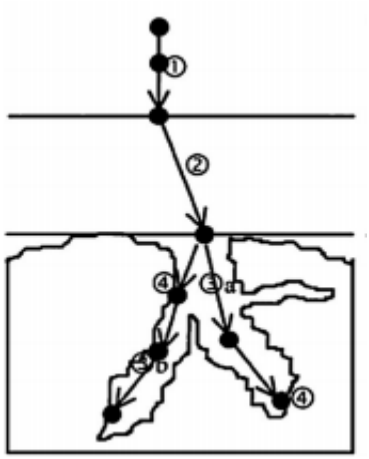
diffusion or by a combination of all [63]. When carrying out adsorption kinetic experiments in a conventional perfectly stirred slurry batch vessel, the relationship between the adsorbate concentration in the liquid (C, mg/L) and in the solid phase (q, mg/g) in every instant can be represented by Eq. 1.2 (which basically results from a mass balance to the adsorbate):

$$q = \frac{(C_0 - C)V}{W} \qquad \text{Eq. 1.2}$$

In this equation, C_0 is the initial concentration of adsorbate in the liquid phase, W (g) is the adsorbent mass and V (L) the solution volume [64].

The adsorption kinetics have been described by several models. The later works divide this phenomenon into three steps (Figure 1.4). The first step can be divided in two and is related to the transportation of the adsorbate to the adsorbent surface: firstly occurs the transportation of adsorbate from the bulk solution to the boundary layer of the solvent. Then, this layer, which corresponds to quiescent water involving the adsorbent particle, must be crossed by the adsorbate through molecular diffusion. The driving force in this case is the concentration difference and the diffusion rate will also depend on the hydrodynamics of the system. The second step corresponds to the intraparticle diffusion with the transport of the adsorbate from the surface of the adsorbent to its sites. It can be divided in two diffusion types: pore diffusion in the macropores/mesopores and surface diffusion in the micropores, and both act in parallel in the interior of the adsorbent particle. The second one is most likely to be significant in porous adsorbents with a high surface area and narrow pores. Intraparticle diffusion is independent of hydrodynamic conditions in a system, but depends on the size and pore structure of the particle. The last step occurs after the transport of the adsorbate to the available site, when the interaction is created and adsorption takes place (physical or chemical adsorption) [46].

Therefore, the overall adsorption process may be controlled either by one or more steps, e.g. film or external diffusion, pore diffusion, surface diffusion and adsorption on the pore surface, or a combination of more than one step. In a rapidly stirred batch, the diffusive mass transfer can be related by an apparent diffusion coefficient, which will (hopefully) fit the experimental sorption rate data.



1. Diffusion/Convection (bulk of solution)

2. External mass transfer (outer layer)

3. Porous and surface diffusion (inside the particle)

4. Adsorption (inside the particle)

Figure 1.4. Diffusion mechanisms involved in the adsorption process [63].

Generally, a process is diffusion-controlled if its rate depends on the rate at which components diffuse towards one another. The possibility of intraparticle diffusion was explored by using the intraparticle diffusion model described by Weber and Morris:

$$q_t = k_d t^{1/2} + I \qquad \text{Eq. 1.3}$$

Here, k_d is the intraparticle diffusion rate constant (mg/(g.min$^{1/2}$)), and I (mg/g) is a constant related to the thickness of the boundary layer: the larger is the value of I, the greater is the boundary layer effect; t stands for time (min) [65].

In 1898, Lagergren proposed a pseudo-first order rate expression for the liquid-solid adsorption system, which is generically expressed as follows for a batch system [66]:

$$-\frac{dn}{dt} = V\frac{dC}{dt} = k_1 W(C - C_e) \qquad \text{Eq. 1.4}$$

Blanchard et al. proposed another model for the analysis of sorption kinetics, the pseudo-second-order. The rate law for this system is expressed as [67]:

$$-\frac{dn}{dt} = V\frac{dC}{dt} = k_2 W(C - C_e)^2 \qquad \text{Eq. 1.5}$$

In these two equations, n (mg) represents the mass of adsorbate in the liquid phase, t (min) the time of contact and k_1(L/g/min) and k_2 (L^2/min/g/mg) the adsorption kinetic constants of pseudo-first and pseudo-second orders, respectively. V stands for the volume of the (liquid-phase) system (L), C for the concentration of the adsorbate in such a phase (mol/L) at time t, C_e the adsorbate concentration in the liquid phase at equilibrium stage (mg/L) and W is the mass of adsorbent [64].

Integrating Eq. 1.4 and Eq. 1.5 between t = 0 and t = t, Eq. 1.6 and Eq. 1.7 are obtained respectively [64]:

$$\ln\left\langle\frac{C-C_e}{C_0-C_e}\right\rangle = -k_1\frac{W}{V}t \qquad \text{Eq. 1.6}$$

$$\mathrm{C} = C_e + \frac{V(C_0-C_{e)}}{V+k_2Wt(C_0-C_{e)}} \qquad \text{Eq. 1.7}$$

Substituting all concentrations of adsorbate in the liquid phase for the ones in the solid phase (through Eq. 1.2), Eq. 1.8 and Eq. 1.9 are obtained, respectively [64]:

$$q = q_e\left(1-\exp\left(-k_1\frac{W}{V}t\right)\right) \qquad \text{Eq.1.8}$$

$$q = \frac{{q_e}^2\left(\frac{W}{V}\right)^2 k_2 t}{1+ q_e\left(\frac{W}{V}\right)^2 k_2 t} \qquad \text{Eq.1.9}$$

Here, the q_e is the equilibrium concentration of adsorbate on the adsorbent (mg/g). Adsorption kinetic models, such as the pseudo-first and pseudo-second order kinetic equations, do not describe individually all the steps of adsorption. When these apparent kinetic models are applied, it is normally assumed that the overall rate of adsorption is exclusively controlled by the adsorption rate of the adsorbate on the adsorbent surface, and both intraparticle diffusion and external mass transport can be neglected [63].

1.8 Adsorption equilibrium and isotherms

The establishment of the most appropriate adsorption equilibrium correlation, i.e. of an equation relating adsorbate concentration in its solvent and in the adsorbent phase, is fundamental to explore novel adsorbents and to find an ideal adsorption system. To predict adsorption performances and perform a quantitative comparison of adsorbents in different systems, adsorption models were created. They describe (or provide an idea) how pollutants interact with the adsorbent materials, and thus are critical for optimization of the adsorption processes, surface properties and capacities of adsorbents, and effective design of the adsorption systems. When an adsorbate-containing phase has been contacted with the adsorbent for sufficient time, adsorption equilibrium is achieved and there is a dynamic equilibrium between the adsorbate concentration in the bulk solution and the interface solution. Among several models, Langmuir and Freundlich are two of the most used models to describe isotherms [68].

The Langmuir model assumes an unimolecular thick layer of adsorbate upon the surface of an homogeneous adsorbent without having any interactions between adsorbed molecules. The mathematical form is given by Eq.1.10:

$$q_e = \frac{q_L.K_L.C_e}{1+K_L C_e} \quad \text{Eq. 1.10}$$

In equation 1.3, q_e (mg/g) and C_e (mg/L) are the equilibrium concentration of adsorbate on the adsorbent and in the solution, respectively, q_L (mg/g) is the maximum monolayer capacity, and K_L (L/mg) is the Langmuir adsorption equilibrium constant [69].

On the other hand, the empiric Freundlich model covers the heterogeneity of the surface and the exponential distribution of sites and their energies. The Freundlich adsorption isotherm is expressed in Eq. 1.11:

$$q_e = K_F C_e^{\frac{1}{n_F}} \quad \text{Eq. 1.11}$$

Here, K_F (mg/g/(mg/L)$^{1/n}$) stands for the adsorption equilibrium constant and n_F is the Freundlich model constant, indicative of the intensity of the adsorption [70]. The Freundlich expression is an exponential equation and, therefore, assumes that as the adsorbate concentration increases, the concentration of adsorbate on the adsorbent surface also increases [71].

The Temkin isotherm assumes that the heat of adsorption of all the molecules in the layer decreases linearly with coverage due to adsorbent–adsorbate interactions, and that the adsorption is characterized by a uniform distribution of the binding energies, up to some maximum binding energy [71]. Temkin model is given by:

$$q_e = \frac{RT}{b}\ln(K_T C_e) \quad \text{Eq. 1.12}$$

In equation 1.12, K_T is the equilibrium binding constant (L/mg), b is related to heat of adsorption (J.g/(mg.mol)), R is the gas constant (8.314 J/K mol) and T is the absolute temperature (K) [72].

Sips isotherm combines the Langmuir and Freundlich equations, leading to a hybrid model able to better describe the heterogenous adsorption systems [68]. Sips isotherm model is given by the following equation:

$$q_e = \frac{q_s K_s {C_e}^{n_s}}{1+K_s {C_e}^{n_s}} \quad \text{Eq. 1.13}$$

In this equation, q_s represents the maximum monolayer adsorption capacity (mg/g), K_s is the Sips constant related to the adsorption energy and n_s can be seen as the parameter characterizing the system heterogeneity [73].

1.9 Adsorbents – Application to 5-FU removal

There are several types of adsorbents and they can have a natural origin or result from an industrial production and/or activation process. Engineered adsorbents can be classified into carbonaceous adsorbents, polymeric adsorbents, oxidic adsorbents and zeolite molecular sieves. Since engineered adsorbents are produced under strict quality control and show nearly constant properties, they exhibit the highest adsorption capacities. On the other hand, natural adsorbents are less expensive, but present a lower adsorption capacity and the properties are subjected to stronger variations [44]. Materials such as activated carbon and zeolites can be specifically engineered with precise pore size distributions and consequently tuned for a particular separation application [74].

A bibliographic review of some adsorbents and their action on 5-FU removal was performed. The use of adsorption as a process to remove 5-FU from water wasn´t carried out by all the authors, although information related to controlled release of 5-FU is more often. Therefore, in order to enrich this work, information about the loading of 5-FU on adsorbents to controlled release in human body purposes (zeolites, fibers and graphene) is also referred. Activated carbon is, by far, the most referred adsorbent for the removal of pollutants from water and one of the most known adsorbents, whereby it will be a special feature in this work. Molecular imprinted polymers are also mentioned for the same goal; however, their use is still recent. Due to the similarity among activated carbon and carbons blacks, they will be mentioned as well. MIPs, fibers and graphene are only mentioned in Appendix A, since they weren't tested in this work, despite their potential to remove 5-FU from waters.

1.9.1 Activated carbon

The use of activated carbon dates back from 1550 B.C. by the Egyptians [49]. Currently, it is mainly used for environmental cleaning purposes, but also in industry in several liquid phase (e.g. decolorization of oils and fats, sugar refining, decaffeination of coffee, gold recovery, among others) and gas phase (e.g. recovery of organic solvents, biogas purifications, gas masks, among others) adsorptions [46]. It can avoid some operational difficulties as slow and/or difficult filtration, retarded and incomplete crystallization, emulsion formation and foaming during concentration and/or distillation [49].

The variance between activated carbons will depend on the material used and the manufacture process applied. The key element for these organic sources is their reliability and constancy. Posteriorly, the manufacturing processes will be so finely tuned that variations in the quality of resource is not acceptable. Collection from separated areas, transportation, bulk availability and seasonal variations in quality and availability are reasons why some resources are not used [58].

In terms of manufacture of activated carbon, it can be divided in two steps: carbonization and activation. Carbonization is a process where organic material is transformed into high carbon content solid residues, usually by pyrolysis in an inert atmosphere [75]. Activation is used for most applications, where some ameliorations related to micropore volume or surface area are necessary, which influence the adsorption capacity [76].

Activated carbon involves a large capital investment and high operating costs when applied in industrial facilities [46]. During the adsorption process, activated carbon loses capacity to adsorb more molecules, since its sites are being occupied. At certain point its utilization is unacceptable and fresh activated carbon is required. Once the carbon is exhausted there are, at least, two options: it is disposed by incineration or land filling, or it can be regenerated for further reutilization [53]. More information about regeneration of activated carbon is available in Appendix A.

Activated carbons include a wide range of amorphous carbon-based materials that can be distinguished from elemental carbon by the oxidation on the outer and inner surfaces of the carbon [77]. Commercial activated carbons brands made by different processes differ in adsorptive characteristics: some carbons can be more specific for an adsorbate and others for a different one [49]. Although this consideration, all these carbonaceous materials are prepared in such a way that they exhibit specific properties to adsorption of several compounds, due to their large specific surface areas (500-1500 m^2/g), well-developed porosity (0.7-1.8 cm^3/g) and tunable surface-containing functional groups, which confer a high adsorption capacity [46].

Besides these characteristics, there are more that may require consideration for some products and processes: density, particle size distribution, moisture content, pH, total ash, filtration rate, oil retention, resistance to attrition, water-extractable inorganics, acid-soluble inorganics, hardness, dustiness, ignition temperature, wettability, electrical conductivity, ash content and content of some compounds as sulfur, sulfides, sulfates, phosphates, iron, copper, zinc, calcium, magnesium and silica [49]. Most of these characteristics are also important in other adsorbents, whereby they were already mentioned in a previous section.

Activated carbons are available in several forms: symmetrical pellets, irregular shaped granules and powder. The pellets are recommended when low resistance to fluid flow is necessary and there are standard sizes, as 1/8 and 3/16 inches. The granular carbons are available in many sizes and use to be expressed in mesh [49]. Granular activated carbon (GAC) is typically used for fixed-bed adsorbers [44]. Relatively to powdered activated carbon (PAC), it is available in very fine particles, used in batch-contact processes. This fine grinding makes the internal surface more readily accessible to molecules of solute, which provides more rapid adsorption, while a larger size is more adequate when low resistance to flow is needed [49]. PAC is mostly used for slurry reactors/adsorbers. The particle size distribution among GAC and PAC can be distinguished as less than 40 μm for PAC and in the range of 0.5 to 4 mm for GAC, although different values are found in literature [44].

Activated carbon contains some ash derived from the raw material, in quantities ranging from 1 to 12 wt%. The ash mainly consists of silica, alumina, iron oxides, and alkaline earth metals. The ash content in the activated carbon increases its hydrophilicity. This is advantageous when PAC is used for water treatment because PAC does not stick on the reactor walls if the ash content is high [78].

1.9.2 Zeolites

Zeolites are crystalline aluminosilicate materials with a three-dimensional structure that forms periodic arrangements of cages and channels of nanometer dimensions. The pores act like filters, allowing preferentially small molecules to fit inside and exclude molecules that are too big. Their tailored structure, stability and activity offer to these materials several applications as molecular sieves, catalysts, adsorbents, among others, with high capacities and selectivity [79] [80].

1.9.3 Case study for activated carbon and zeolites

Kovalova et al. (2013) performed an adsorption study with two powdered activated carbons to assess the removal of the polar pharmaceutical 5-FU from ultrapure water and a wastewater treatment plant effluent. Table 1.3 presents the operating conditions and the carbons characteristics. The operating conditions used in these experiments are close to real scenarios.

Table 1.3. Characteristics and operating conditions of the activated carbons used to treat water contaminated with 5-FU [50].

Adsorbent	pI[a]	Surface area (m^2/g)	Particle size D50 (μm)	Raw material	Matrix	[adsorbent] (mg/L)	$[5\text{-FU}]_0$ (mg/L)	T (^0C)	pH
SAE Super	9.8	1300	15	Peat/wood	WWTP effluent TOC=5mg/L σ=1,2 mS/cm	220	0.2	20	7.8
HOK Super	10	300	24	Lignite		500			

Notes: pI -Isoelectric point; T –Temperature.

On the other hand, Datt et al. (2015) tested the viability of zeolites as vehicles for controlled release of 5-FU in human body. Therefore, the concentration of 5-FU involved in the experiments is completely different from the ones presented for activated carbon and from the targets of real waters. It is noteworthy that no other studies were found in the literature concerning the application of zeolites as adsorbents of 5-FU molecule. Essentially, the differences between the zeolites studied are the SiO_2/Al_2O_3 ratios, which will bear implication in pore volume and surface area: aluminium may interact with the 5-FU species by hydrogen bonding of the carbonyl oxygen atoms with the zeolite hydroxyl groups, also through coordination between the drug molecules and the aluminium atoms. Therefore, increasing the SiO_2/Al_2O_3 ratio, 5-FU loading will increase as well. Important information as the adsorbent concentration was not defined at the operating conditions.

The values of adsorption capacity were not mentioned by the authors. Therefore, the adsorption capacities were estimated using the concentration of adsorbent and 5-FU, as well as the efficiency of the process (95%) – Table 1.4. For zeolites, adsorption capacity was obtain through a thermogravimetric analyzes (TGA). In fact, the article refers it as loading capacity, which is not the same of adsorption capacity, but allows a prediction of it. In order to avoid an incorrect quantification, the excess of 5-FU was previously removed from zeolites through a wash with water.

Table 1.4. Characteristics and operating conditions of the zeolites used to loading and realize of 5-FU [81] [82].

Adsorbent	SiO_2/Al_2O_3 ratio	Nominal cation form	Pore volume (cm^3/g)	Surface area (m^2/g)	Matrix	$[5\text{-FU}]_0$ (mg/L)	T (^0C)
CBV 100	5	Hydrogen	0.26	594	Water	12000	20
CBV 720	30	Hydrogen	0.30	688			
CBV 760	60	Hydrogen	0.31	711			

Observing Table 1.5, both carbons are described by the same kinetic model and isotherm and it has been verified an increase of adsorption capacity when the carbon surface area is higher (Table 1.3). Homogeneous surface diffusion model (HSDM) is a frequently used model. It predicts the diffusion of a molecule from the external surface of the adsorbent particle through the pore surface to the adsorption site and assumes that internal mass transfer is only due to surface diffusion with the pore volume diffusion resistance negligible [63].

Table 1.5. Adsorption properties of activated carbon and zeolites [81] [50].

Adsorbent		Equilibrium time (min)	Adsorption capacity (mg/g)	Kinetic model	Isotherm model
Activated carbon	SAE Super	300	0.86	HSDM model	Freundlich
	HOK Super		0.38		
Zeolite	CBV 100	-	110	-	-
	CBV 720		100		
	CBV 760		90		

For zeolites, they have a high capacity to uptake 5-FU, although is necessary to be into account the enormous concentration of 5-FU used in this experiment. In terms of superficial area of zeolites (Table 1.4), the values are among the two superficial areas found on activated carbons, whereby adsorption capacity of zeolites may be higher than activated carbons, because of its nature based on aluminum and silica. Comparing the two kinds of materials, it is clearly the difference between the adsorption capacities of adsorbents used for cleaning purposes (activated carbons) and the adsorbents used for health care (zeolites). The operating conditions used maybe are the reason of such difference.

1.9.4 Carbon blacks

Carbon blacks production is a significant modern industry. It started at the period up to about 1940, when there was a significant expansion of the carbon black industry associated with the growth in size and number of newspapers and printing in general. This period of history saw increasing number of petrol-driven vehicles on the roads, all requiring pneumatic tyres which incorporated carbon blacks to promote wear resistance [58].

Among carbon materials, carbon blacks are one of the most common raw chemical materials and are used as reinforcing filler for rubber goods in tire manufacturing and as pigment for printing inks, coatings and plastics [83]. Plants for the manufacture of carbon black are strategically located

worldwide to supply the rubber tyre industry, which consumes 70% of the carbon black production. About 20% is used for other rubber products and 10% is used for a variety of non-rubber applications [84]. Industrially, the vast market of newspaper, magazine and book production is dependent on the carbon black as the ink source [58].

As activated carbon, carbon blacks belong to the family of carbons. They all come from organic parent sources, but with different carbonization and manufacturing processes. Carbon blacks are formed by the incomplete combustion of fossil fuels or by thermal decomposition of hydrocarbons and the formation of carbon blacks depends on either the presence or absence of oxygen. In industry, carbon blacks are mainly manufactured using the furnace and channel processes. The furnace process, which is the predominant method for the thermal cracking and the production of carbon blacks, has been used to meet the demands of the rubber industry for such a long time. This continuous process is operated in a closed reactor and produces a large amount of polluting emissions, including COx, SOx and NOx [83]. Manufacturers of carbon blacks produce at least 70 products designed for specific applications. Carbon blacks are supplied by manufacturers both as powders and as pellets. They are classified as furnace blacks (<50 nm diameter), acetylene blacks (40-55 nm diameter) and thermal blacks (100-500 nm diameter) [58].

There are four fundamental properties of carbon blacks which determine how these materials can be used upon proper optimization. Firstly, their fineness and particle size distribution, which influence blackness and tint. Secondly, structure within the carbon black particle and the aggregation of the particles, influencing their dispersibility and electrical conductivity. Porosity and pore-size distributions affect viscosity and coverage requirements. Finally, the presence of surface functionality, which influences wettability, viscosity and electrical conductivity; in carbon black usage, it is their external surface, with oxygen functionality in some cases, which dominates their "sorption" properties, distinctly from the internal microporosity as found in activated carbons [58].

Finally, it should be remarked that no studies were found in the open scientific literature regarding the use of carbon black for the removal of 5-FU from aqueous matrices.

1.10 Aim of the thesis

The main objective of this thesis was to test some adsorbent materials due to their potential for the intended application and availability at the research group (though specific collaborations detailed in the acknowledgements section), namely activated carbons, carbon blacks and zeolites, for 5-FU removal from water, as first step of a combined methodology which aims to treat waters contaminated with 5-FU.

2 Materials and methods

2.1 Reagents and Materials

5-FU with a purity of 97.7% (w/w) was purchased from Sigma-Aldrich (St. Louis, MO, USA). For the adsorption and kinetics assays, four commercial activated carbons (CECA, Merck, Norit and Wittco), two carbon blacks (BP2000 and Vulcan XC72) and six zeolites (CZB 25, CZM 20, CZP 30, CZP 90, CP814C and P-38) were used. The carbonaceous materials were kindly provided by Professor Francisco Maldonado-Hódar, from the University of Granada (Spain), while zeolites by Professor Alírio Rodrigues, from LSRE – Faculty of Engineering, University of Porto. The distilled water used to prepare 5-FU solutions was filtered through 0.45 μm nylon membrane filters obtained from Supelco, Sigma-Aldrich (Pennsylvanis, USA). Syringe filters with 0.2 μm PTFE membrane were purchased from VWR (Wester Chester, USA) and high precision cell made of Quartz Suprasil® with 10 mm by Hellma Analytics.

2.2 Standards and adsorbents preparation

A 5-FU stock solution of 250 mg/L was prepared by dissolving the appropriate amount of powder in filtered distilled water. The stock solution was used to prepare working solutions with different 5-FU concentrations (1.0, 2.5, 5.0, 7.5 and 10 mg/L). All solutions were preserved by refrigeration until their use.

The six carbonaceous materials and the six zeolites were grinded and sieved, in order to obtain particle sizes in the range of 38–63 μm and 216-600 μm. The adsorbents were dried at 110 °C for 24 h, after which they were kept in a desiccator.

2.3 Adsorption kinetics runs

To obtain the desired adsorbent concentration, an appropriate amount of each adsorbent was added to 500 mL erlenmeyers. The wet mass was weighted, although the mass of water, previously quantified, was taken into account and retired from the final value of the mass. The erlenmeyers were placed in an OLS200 orbital/linear shaking bath and 5-FU solutions at different concentrations (1 mg/L and 10 mg/L) were added. It is noteworthy that 5-FU solutions were previously heated to the desired temperature. OLS200 was purchased from Grant Instruments (Shepreth, Cambridgeshire) and it consists on a combined orbital/linear thermostatically-controlled shaking water bath, which allows the control of agitation (88 rpm, unless otherwise specified) and temperature (30 °C). Samples of 1 mL were withdrawn during the experiment over time, filtered

through syringe filter and collected in vials. The vials with the solutions were preserved in a freezer for further analysis.

2.4 Adsorption equilibrium runs

The equilibrium runs were carried out in a similar way to kinetic experiments. A given amount of adsorbent was put in contact with different 5-FU concentrations and samples were collected at the beginning (t = 0) and after 24 h (equilibrium conditions). Then, the samples were centrifuged in an Eppendorf® Minispin® from Sigma-Aldrich at 3000 rpm during 5 minutes. The resulted supernatant was kept in vials and preserved in a freezer for further analysis.

2.5 Spectrophotometric analysis of 5-FU

The 5-Fu adsorption was followed by UV-Vis spectrophotometry. This analytical technique exploits interactions between radiation and materials, in particular the absorption phenomenon. During the experiments, absorbance was measured at 266 nm (which is the characteristic wavelength for 5-FU molecule) in a Helios gamma UV-Vis spectrophotometer from Thermo Electron Corporation. Calibration curve was constructed for 5-FU standards in water, in the range 0.15 -12.5 mg/L.

2.6 Storage, fate and treatment of wastes

Liquid and solid wastes containing 5-FU were generated during the experimental activity. These wastes were collected appropriately to be treated further by a specific system through different specialized entities – solid wastes by Ambimed and liquid wastes by Sistema de Gestão Ambiental da FEUP (EcoFEUP).

3 Results and discussion

3.1 Validation of the analytical method

The first step of this work was to validate the analytical methodology using UV-Vis spectrophotometry for the determination of 5-FU in aqueous samples, ensuring an accurate, specific, reproducible and robust analytical method under a specific range in which the analyte will be analyzed. As referred in chapter 1, 5-FU has a maximum UV radiation absorption between 265 and 266 nm, whereby 266 nm was used for analysis. Linearity, precision and accuracy were used to guarantee the acceptability of the analytical method.

3.1.1 Linearity range and limits of detection and quantification

The calibration was performed at ten concentration levels, in the range of 0.15 – 12.5 mg/L of 5-FU in filtered distilled water, being each standard solution analyzed in duplicate. Figure 3.1 shows the calibration curve of 5-FU and presents the linearity parameters (slope, interception and related confidence limits (95%, *t*-student distribution)).

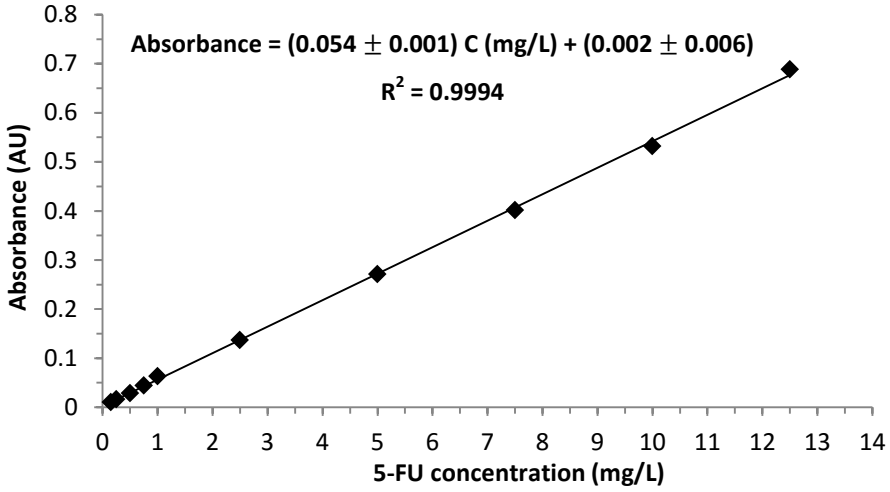


Figure 3.1. Calibration curve for 5-Fu quantification in water by UV-Vis spectrophotometry.

The slope, interception and correlation coefficient obtained by the linear least squares regression treatment are presented in Table 3.1, along with the standard deviation of residuals ($S_{y/x}$), of intercept (S_a), and of slope (S_b),as well as the limit of detection (LOD) and the limit of quantification (LOQ) [85]. Although the correlation coefficient is higher than the recommended (>0.995), the limits of detection (LOD) and quantification (LOQ), calculated as 3× and 10× the standard deviation of the intercept plus the intercept, were higher than the lowest concentration

level. However, if LOD and LOQ are calculated using the signal-to-noise ratio of 3 and 10, respectively, the results were even worst, so this estimation mode was discarded. In this case, the lowest concentration (0.15 mg/L) was considered as the LOQ. This fact is expected because the UV-Vis spectrophotometer is not the preferable analytical method when trace amounts are expected. However, it is considered acceptable for the subsequent analysis because is simple and fast, and implies a lower cost as compared with other techniques (e.g., liquid chromatography, capillary electrophoresis, Immunoassay) [86].

Table 3.1. Quantitative parameters for the determination of 5-Fu in water by UV-Vis spectrophotometry.

Linearity range (mg/L)	Slope (AU.L/mg)	Intercept (AU)	R[a]	$S_{y/x}$[b]	S_a[c]	S_b[d]	LOD[e] (mg/L)	LOQ[f] (mg/L)
0.15-10	5.39×10^{-2}	2.37×10^{-3}	0.999	6.33×10^{-3}	2.37×10^{-3}	2.74×10^{-3}	0.15	0.51

Notes: [a] Correlation coefficient; [b] Standard deviation of residuals; [c] Standard deviation of intercept; [d] Standard deviation of slope; [e] Limit of detection; [f] Limit of quantification.

The quality control laboratories typically use three criteria for admitting that a method is suitable for use in analysis [85]: a) relative standard deviation of the slope (s_a/a) should be lesser than 5%; b) interception should contains the origin ($b-s_a < 0 < b + s_a$); c) the correlation coefficient of the calibration curve should be greater than 0.995. Therefore, it can be concluded that the calibration curve is suitable for the purpose of this analysis, since it meets all the criteria specified above: the relative standard deviation of the slope was 0.86%, the correlation coefficient of the calibration curve was 0.999, and the confidence limits for the interception contain the origin.

3.1.2 Precision

The precision can be defined as the degree of scatter between a series of measurements of the same sample. Precision is expressed as the relative standard deviation in percentage (RSD%). In this study, precision was evaluated by repeatability and intermediate precision [87]. The repeatability was evaluated by injection of three 5-FU standard solutions (1.0, 5.0 and 10 mg /L) six times in the same day and under the same conditions (intra-day test). The intermediate precision was evaluated by injection of the same standard solutions in 6 different days (inter-day). The results of precision (expressed as relative standard deviation) are presented in Table 3.2.

Table 3.2. Repeatability and intermediate precision for the determination of 5-Fu in water by UV-Vis spectrophotometry.

n = 6	5-FU concentration (mg/L)		
	1.0	**5.0**	**10**
Repeatability (RSD%)	9.63	0.81	0.22
Intermediate Precision (RSD%)	6.23	0.96	1.15

The results showed that there are higher variations in the response for lower 5-Fu concentrations than for higher ones. For the concentrations of 5.0 and 10 mg/L, values well below 10% were achieved, while for 1.0 mg/L they weren't so good, but still acceptable.

3.1.3 Accuracy

The accuracy can be defined as the closeness of agreement among the conventional true value or an accepted value and the value found. Accuracy was assessed by calculating the percentage of recovery of the analyte at three different concentrations (1.0, 5.0 and 10 mg/L). These solutions correspond to different samples, prepared in order to approach the actual samples (i.e., with concentration within the range of the adsorption study) and enter into account possible interferences. During adsorption experiments, the contact of adsorbent materials with water could lead to the leaching of some species or compounds that may interfere in the 5-FU analytical response by UV-Vis spectrophotometry. Therefore, solutions of the six types of carbonaceous materials (BP2000, CECA, Merck, Norit, Vulcan XC72 and Wittco) were prepared in distilled water, at the same concentrations used in adsorption experiments (90 mg/L for CECA, Vulcan XC72 and Wittco, 60 mg/l for BP2000 and Norit and 40 mg/L for Merck). After 24 h, which corresponds to the maximum time that the materials were left in contact with water, the solutions were filtered and the filtrated was used to prepare 5-FU solutions of 1.0, 5.0 and 10 mg/L. The analytical responses obtained were compared to the corresponding standards prepared in filtered distilled water. The retention of 5-FU in the syringe filter has been previously studied by Mariana Carvalho [88], and it was concluded that none 5-FU is retained. The accuracy was estimated through analytical recovery tests and the results are summarized in table 3.3.

The good recovery results (on average 100.3%) enable a reliable quantification of 5-FU in the tested conditions, even at the lowest contamination level assessed. In this manner, all the validation parameters (linearity, detection and quantification limits, precision and accuracy) allowed the validation of the method for the specific purpose of analysis of 5-FU in adsorption experiments.

Table 3.3. Evaluation of the accuracy of the UV-Vis spectrophotometry method for the determination of 5-Fu in water (values in %).

Recovery (n = 3)	5-FU concentration (mg/L)		
	1.0	5.0	10
Aqueous solution in contact with:			
BP2000	104 ± 1	102.6 ± 0.2	98.3 ± 0.2
CECA	99 ± 1	97.7 ± 0.3	98.3 ± 0.3
Merck	110 ± 2	101.1 ± 0.3	98.6 ± 0.1
Norit	96.8 ± 0.9	100.1 ± 0.3	98.4 ± 0.1
Vulcan XC72	103 ± 2	99.1 ± 0.2	99.8 ± 0.1
Wittco	104 ± 1	98.5 ± 0.2	96.4 ± 0.1

3.2 Setting of adsorption conditions – preliminary runs

There are several factors influencing the adsorption process, although adsorbent and adsorbate concentration are the most important of all. The choice of both should take into account the purpose of the work and the sensitivity of the analytical method used to quantify the analyte.

In the previous section, it was verified that it is not feasible to work at 5-FU concentrations below 0.15 mg/L, whereby it is necessary that the lowest concentration at the end of adsorption process should be at least 0.15 mg/L. Thus, concentrations of 5-FU were stipulated in the range of 1.0 to 10 mg/L and adsorbent concentrations were managed from that.

For the preliminary adsorption tests, one kind of carbonaceous materials (Merck) and one of zeolites (P-38) were chosen at the concentration of 500 mg/L (Figure 3.2a). Since the lowest concentration of 5-FU is the critical concentration, due to the analytical method, 1.0 mg/L was used. It was verified that while Merck adsorbed all 5-FU present in water in less than 50 min, P-38 didn't adsorb any even after 5 h. The result for zeolite is not in line with the literature, where relatively high adsorption percentages are reported [81]. However, it should be taken into account that the available studies are related with controlled-release of the drug in the human body, where very different conditions are employed. Additionally, this experiment was only performed for one zeolite and not for others. Therefore, a new assay was carried out for all zeolites at much higher adsorbent concentration (4000 mg/L) (Figure 3.2b). It is noticed that 5-FU is still almost not adsorbed by these materials, even at this extreme adsorbent concentration. For this reason, the study of zeolites was discarded from this work. The properties of the zeolites used are present at Appendix C.

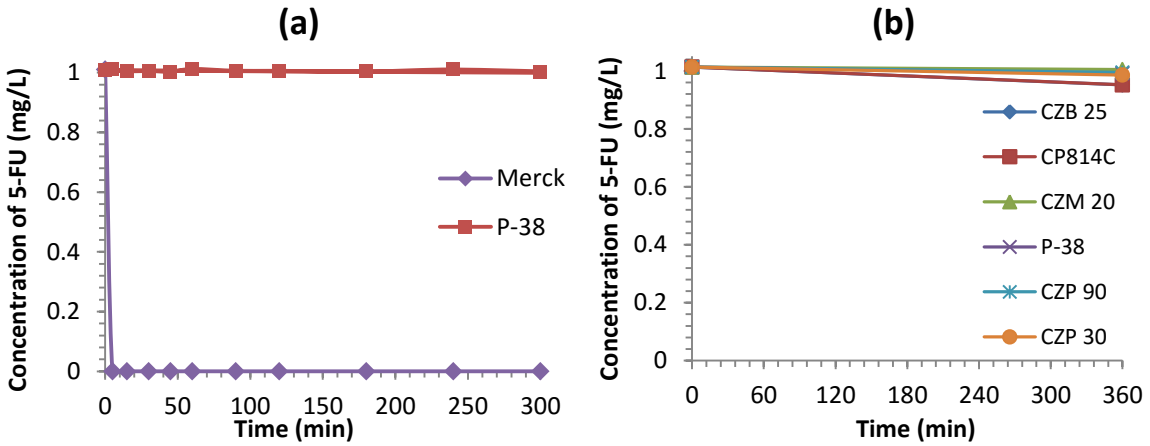


Figure 3.2. Adsorption of 5-FU on activated carbon (Merck) and zeolite (P-38) for an adsorbent concentration of 500 mg/L (a) and 5-FU adsorption on all zeolites (CZB 25, CP814C, CZM 20, P-38, CZP 90 and CZP 30) for an adsorbent concentration of 4000 mg/L (b) ([5-FU] = 1.0 mg/L, particle size = 212 – 600 µm, T = 30 ^{o}C, agitation = 88 rpm)

3.3 Characterization of the carbon-based materials

A series of commercial carbon-based samples, four activated carbons and two carbon blacks, were used for the adsorption of 5-FU. Because their characteristics strongly depend on the raw materials and the thermal activation process followed for the preparation, data sometimes are not provided by the producers. Therefore, some chemical and textural characterization was carried out. All the characterization data was kindly provided by Professor Francisco Maldonado-Hódar from University of Granada (Spain), as well as the carbonaceous materials.

The textural characteristics of the adsorbents are summarized in Table 3.5. They were obtained through N_2 and CO_2 adsorption isotherms at −196 ^{o}C and 0 ^{o}C, respectively, using a Quantachrome Autosorb-1 equipment. The BET and Dubinin–Radushkevich equations were applied to determine the apparent surface area (S_{BET}) and the micropore volume (V_{mic}) and the mean micropore width (L_0) respectively. It is well known that N_2 and CO_2 adsorption isotherms provide complementary information about microporosity. Thus, the narrow microporosity, corresponding to micropores with diameter lower than 0.7 nm, is determined by CO_2, while the total microporosity is obtained from N_2 isotherm in absence of diffusion restrictions. Thus, the volume of N_2 adsorbed close to saturation (P/P_0 = 0.95; $V_{0.95}$) was considered as the total pore volume of the samples. A broad pore size distribution is obtained also by analyzing the N_2 adsorption isotherms in different adsorption ranges: $0.0 < P/P_0 < 0.1$ corresponds to the adsorption into primary micropores (smaller than 0.8 nm), $0.1 < P/P_0 < 0.4$ into secondary micropores (0.8 – 2 nm), and $0.4 < P/P_0 < 0.95$ corresponds to the adsorption in mesopores. All the N_2-adsorption

isotherms obtained correspond mainly to type I (Figure 3.3), pointing out that activated carbons (Merck, Norit, Wittco and CECA) are microporous materials. Nevertheless, the slope of the final plateau of the isotherm, and the apparition of small hysteresis cycles, are indicative of a certain mesoporous volume in activated carbons. On the other hand, the large and open neck of the isotherms corresponding to the CECA samples denotes a high heterogeneity of the microporosity regarding others carbons, with the Wittco sample showing the contrary behavior. It is also noteworthy that in all cases $Vmic(N_2) > Vmic(CO_2)$; this fact, together the large L_0 values obtained, indicates that in general microporosity is large enough to avoid diffusion restrictions of 5-FU (95.34 $Å^3$) to the interior of the narrowest micropores. On the contrary, in general, the adsorption of N_2 is favored regarding the CO_2 one by the contribution of N_2 molecules adsorbed into mesopores.

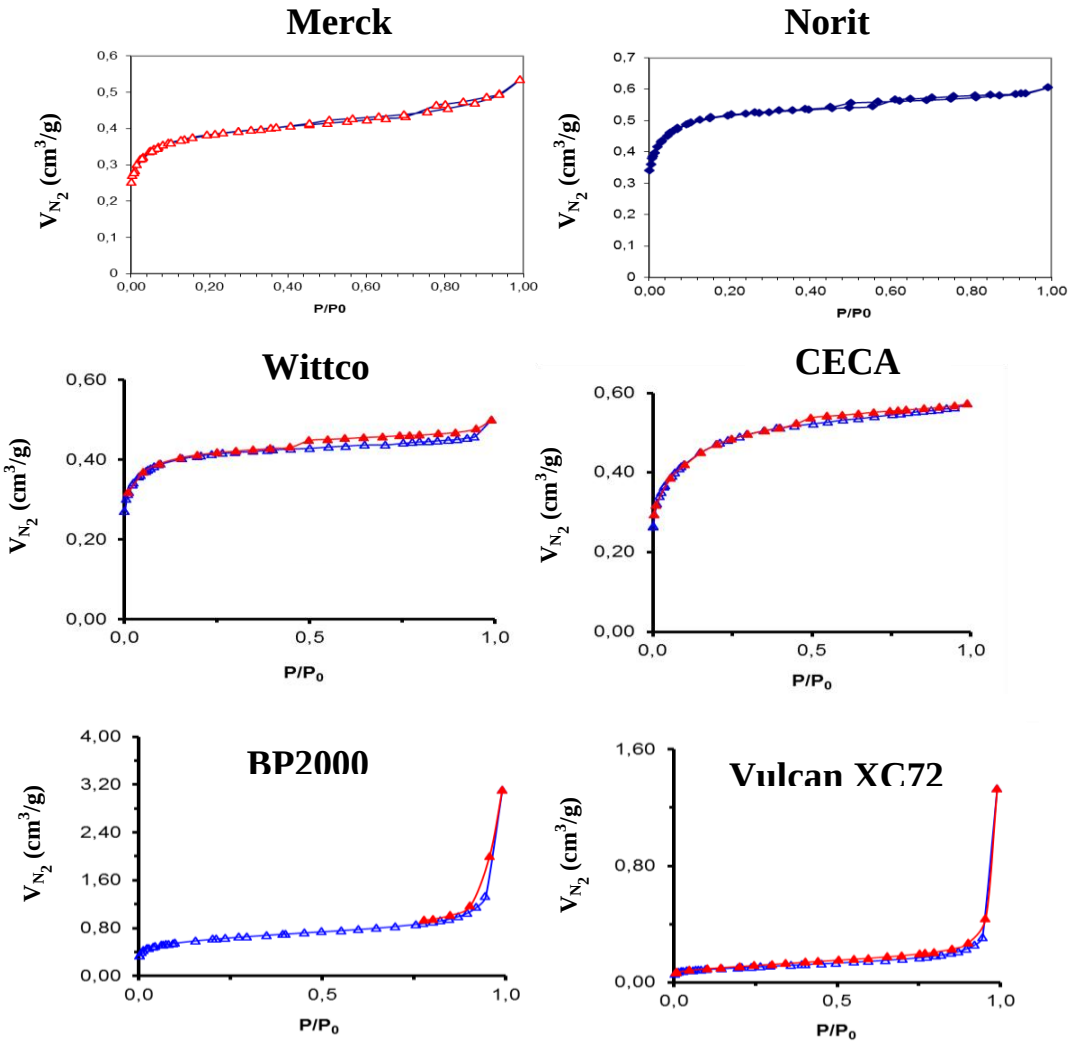


Figure 3.3. N_2 adsorption isotherms of carbonaceous materials. Blue and red lines correspond to adsorption and desorption process, respectively.

The shape of the isotherms strongly changes when analyzing both carbon blacks (Figure 3.3). For the case of Vulcan XC72, the micropore volume (amount of N_2 adsorbed at low P/P_0) strongly decreased regarding the previously described activated carbons. After that, the isotherms present slow slope of up to $P/P_0 > 0.8$, where a very fast increase of the adsorption capacity is observed. It is noteworthy however the high adsorption capacity of BP2000 regarding Vulcan XC72, in spite of the similar nature. Thus, the very high mesopore volume strongly favors the surface area of BP2000 (Table 3.4). In both cases, the application of the BJH method to the desorption isotherms confirms that the main porosity of BP2000 is located in large mesopores and macropores, corresponding in general to pores of diameter larger than 10 nm (Figure 3.4), which probably includes the interparticle voids.

Table 3.4. Textual characteristics of the carbonaceous materials.

Adsorbent material		S_{BET} (m^2/g)	V_{micro} (N_2) (cm^3/g)	V_{micro} (CO_2) (cm^3/g)	L_0 (N_2) (nm)	V_{meso} (cm^3/g)	V_{Total} (cm^3/g)
Carbon blacks	BP2000	1401	0.55	0.26	1.64	2.41	3.11
	Vulcan XC72	228	0.09	0.05	1.92	1.21	1.33
Activated carbons	CECA	1073	0.40	0.25	1.45	0.06	0.57
	Merck	907	0.37	0.24	1.53	0.10	0.43
	Norit	1233	0.54	0.27	1.67	0.06	0.49
	Wittco	999	0.41	-	1.88	0.08	0.50

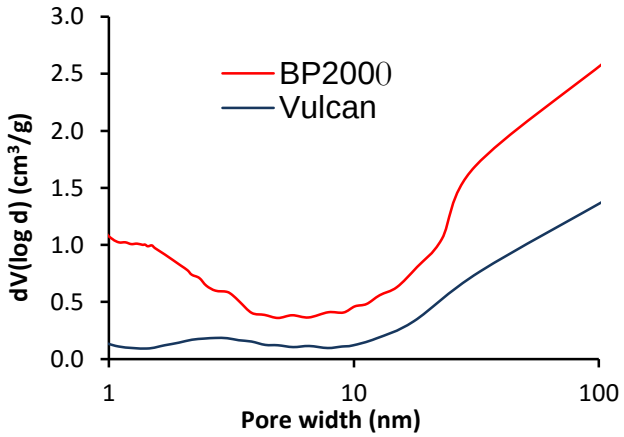


Figure 3.4. Pore size distribution obtained by applying the BJH method to the N_2-adsorption isotherms of carbon blacks BP2000 and Vulcan XC72.

The moisture percentage of each material was also analyzed, being the results present in Table 3.5. In general, the percentage of moisture is low in all the carbon materials, although it is notorious the lower moisture content of carbon blacks compared with activated carbons.

Table 3.5. Moisture percentage of the carbonaceous materials.

Adsorbent material	BP2000	CECA	Merck	Norit	Vulcan XC72	Wittco
Moisture (%)	0.2%	2.1%	2.7%	2.1%	0.2%	2.4%

3.4 Adsorption kinetic runs

After the assay with Merck at 500 mg/L (section 3.2), experiments using lower adsorbent concentrations were performed for all carbonaceous materials taking into account the limit of detection of the method. After a series of trial and error tests, it was possible to achieve apppropriate concentration levels for the different materials (Table 3.6).

Table 3.6. Adsorbent concentrations used in 5-FU adsorption experiments.

Adsorbent material	BP2000	CECA	Merck	Norit	Vulcan XC72	Wittco
Adsorbent concentration (mg/L)	60	90	40	60	90	90

Data of adsorption experiments are shown in Figure 3.5. As expected, in most cases a decreasing adsorption rate (decreasing slope) is observed over time. This phenomenon is due to the decrease of the concentration driving force as a result of 5-FU accumulation on the phase. At the initial stage, the adsorption of 5-FU is fast due to the availability of a large number of surface sites. However, the adsorption gradually became slower until it tends to reaches the equilibrium (if observed), where no more 5-FU can be adsorbed on the solid. At this point, the remaining surface of sites was difficult to be filled and the repulsion between the solute molecules of the solid and bulk phases occurred [89].

Simple kinetic models (such as pseudo-first and pseudo-second order, equations Eq.1.8 and Eq.1.9, respectively) were considered to describe the experimental results of 5-FU adsorption on the carbonaceous materials. The parameters of the kinetic models were determined by fitting the models to the experimental data by a non-linear regression analysis. The best fit was determined applying the mathematical/model selection criterion (MSC) [64]. Besides the correlation between the experimental data and the theoretical results, MSC also takes into account the number of experimental points and the number of parameters of the fitted model. A higher number for MSC is synonym of a better fit. MSC can be represented as:

$$MSC = ln\left[\frac{\sum_{t=1}^{m}(q_{meas}-\bar{q}_{meas})^2}{\sum_{t=1}^{m}(q_{meas}-q_{calc})^2}\right] - \frac{2p}{m} \qquad \text{Eq.3.1}$$

In this equation, q_{calc} is the calculated adsorbate concentration in the solid phase and q_{meas} is the measured adsorbate concentration in the solid phase, $\bar{q}_{meas}$ is the mean of the measured adsorbate concentration in the solid phase, m is the number of experimental points and p is the number of fitting parameters.

Results from kinetic experiments indicate that the adsorption of 5-FU on carbonaceous materials strongly depends on the type of adsorbent and on the initial concentration of 5-FU, among other parameters described below. The results obtained are compiled in Table 3.7 and shown in Figure 3.5.

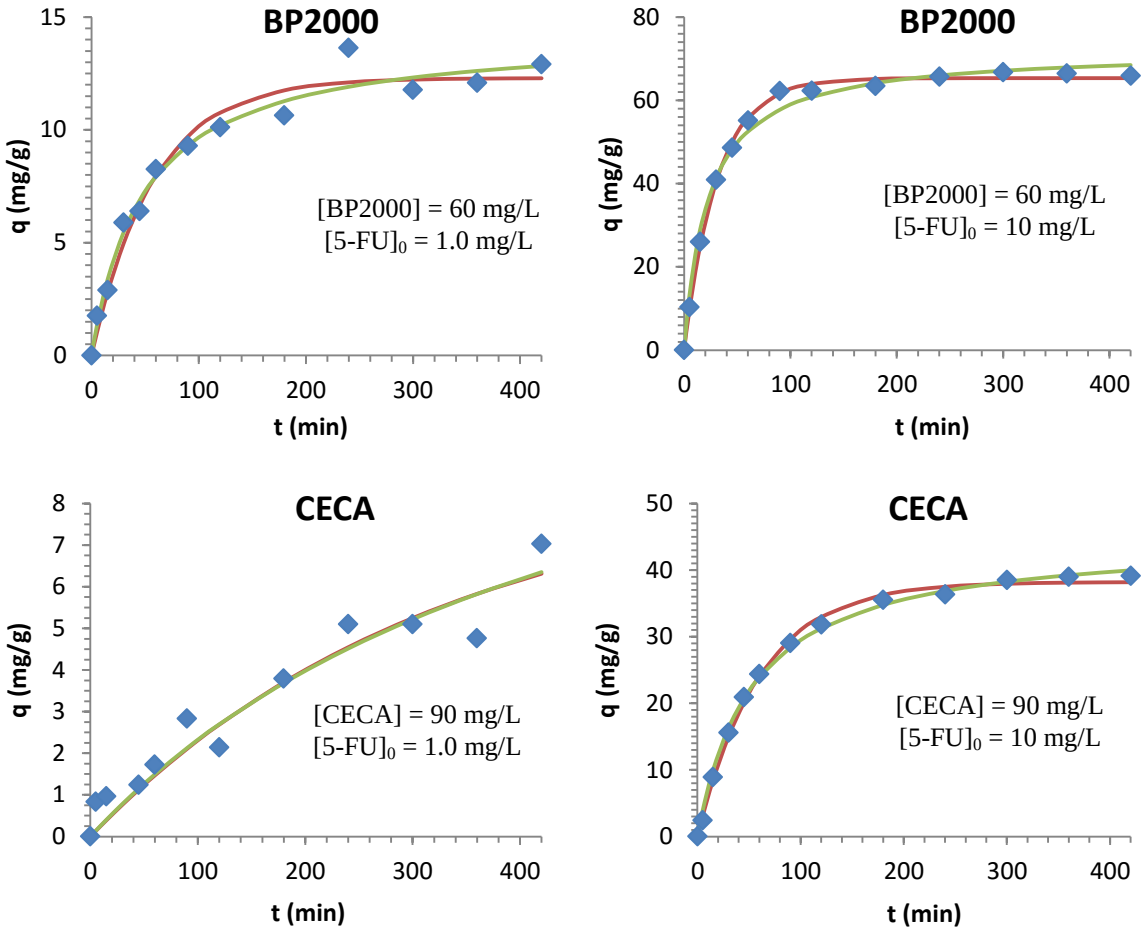


Figure 3.5. Adsorption of 5-FU on BP 2000, CECA, Merck, Norit, Vulcan XC72 and Wittco for a 5-FU initial concentration of 1.0 mg/L and 10 mg/L (T = 30.0 ± 0.1 °C, agitation = 88 rpm, particle size = 212-600 µm). Red and green lines correspond to the pseudo-first order and pseudo-second order models fitting, respectively (continued).

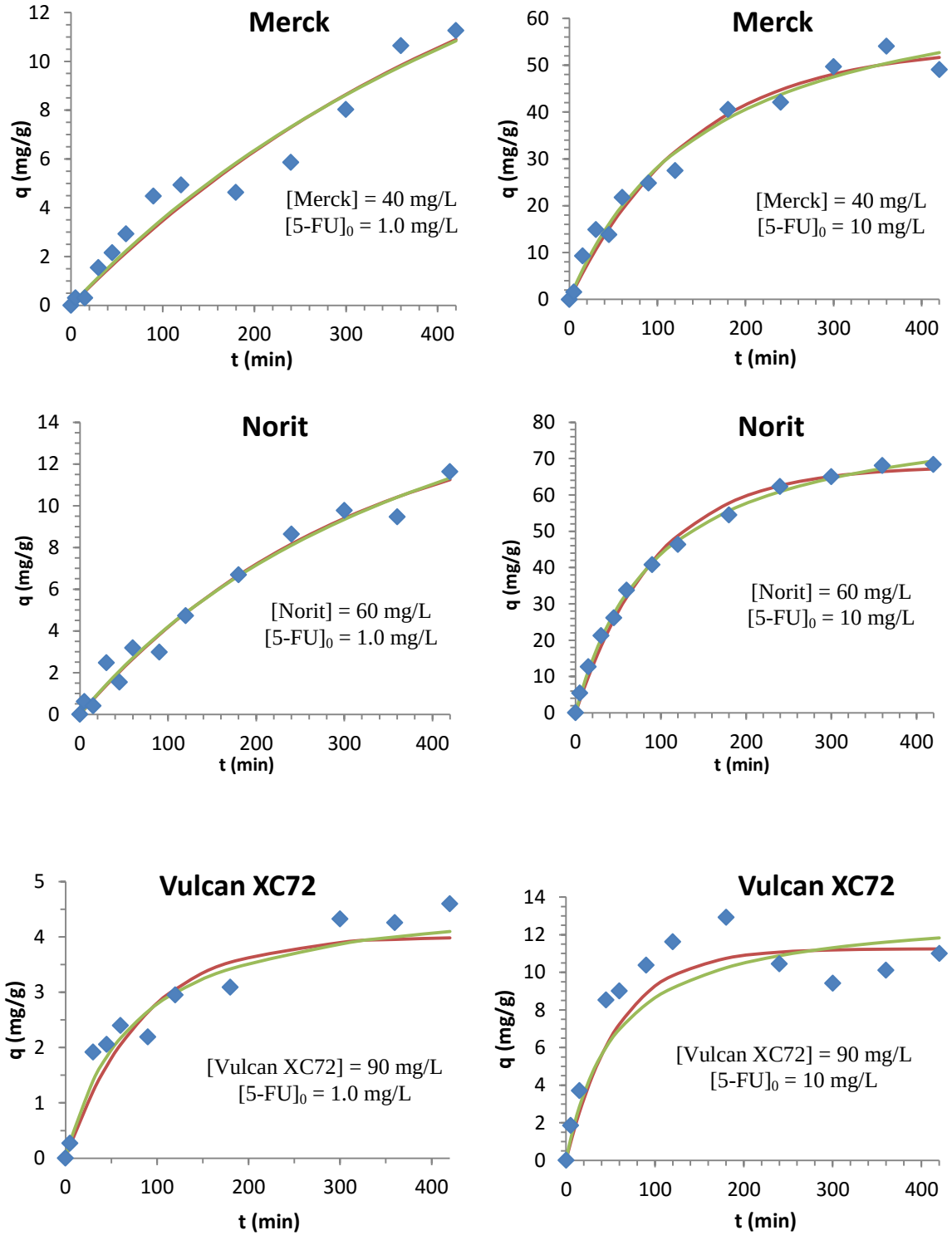


Figure 3.5. Adsorption of 5-FU on BP 2000, CECA, Merck, Norit, Vulcan XC72 and Wittco for a 5-FU initial concentration of 1.0 mg/L and 10 mg/L (T = 30.0 ± 0.1 °C, agitation = 88 rpm, particle size = 212-600 µm). Red and green lines correspond to the pseudo-first order and pseudo-second order models fitting, respectively (continued).

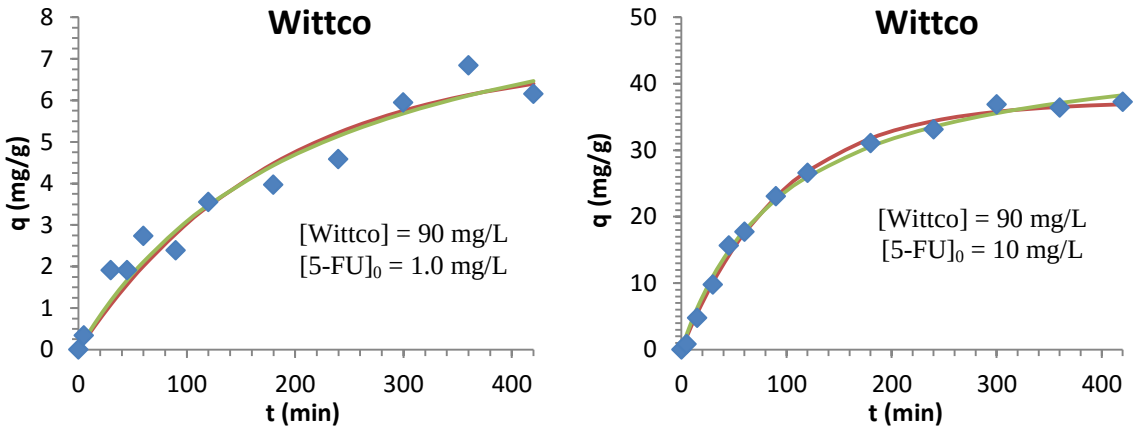


Figure 3.5. Adsorption of 5-FU on BP 2000, CECA, Merck, Norit, Vulcan XC72 and Wittco for a 5-FU initial concentration of 1.0 mg/L and 10 mg/L (T = 30.0 ± 0.1 °C, agitation = 88 rpm, particle size = 212-600 µm). Red and green lines correspond to the pseudo-first order and pseudo-second order models fitting, respectively.

Table 3.7. Kinetic parameters for adsorption of 5-FU on carbonaceous materials (T = 30 ± 0.1 °C, agitation = 88 rpm, particle size = 212-600 µm). In bold are highlighted the best model for each situation.

Adsorbent material	Adsorption reaction models						
		Pseudo-first order model			Pseudo-second order model		
	$[5\text{-FU}]_0$ (mg/L)	q_e (mg/g)	k_1 (L/g/min)	MSC	q_e (mg/g)	k_2 (L^2/g/min/mg)	MSC
BP2000 (60 mg/L)	1	12.30	0.29	3.31	14.31	0.40	**3.56**
	10	65.34	0.53	**5.84**	72.13	0.17	4.42
CECA (90 mg/L)	1	8.69	0.03	2.07	13.87	0.02	**2.07**
	10	38.22	0.18	5.48	45.02	0.05	**5.60**
Merck (40 mg/L)	1	19.32	0.05	2.73	30.28	0.03	**2.76**
	10	54.23	0.18	3.53	72.45	0.06	**3.61**
Norit (60 mg/L)	1	15.20	0.05	**3.56**	24.15	0.02	3.55
	10	67.98	0.18	4.75	85.07	0.03	**6.07**
Vulcan XC72 (90 mg/L)	1	4.01	0.13	2.16	4.81	0.35	**2.58**
	10	11.25	0.19	**0.76**	13.39	0.17	0.65
Wittco (90 mg/L)	1	7.08	0.06	2.66	9.84	0.06	**2.74**
	10	37.36	0.12	**5.39**	47.24	0.03	5.05

First of all, by Figure 3.5 it is verified that equilibrium isn't achieve after 7 hours of contact time for CECA, Merck, Norit, and Wittco at 1 mg/L of 5-FU, while the others demonstrate a faster kinetics. Both pseudo-first and pseudo-second order kinetic models exhibit good adherence to the experimental results. Observing the MSC values obtained for each situation, there isn't a best general model. It seems that the most adequate model slightly depends on the type of material and

on the initial concentration of 5-FU. However, it is noteworthy that the differences between pseudo-first and pseudo-second fits are very smooth for all situations.

By the Table 3.7, it is verified that only CECA and Merck have a defined kinetic model for both 5-FU initial concentrations, while the others vary without any apparent criteria related to the pollutant concentration. Analyzing more in depth the MSC values, it is noticed that the majority of the carbons is described by pseudo-second order. Furthermore, it is verified that, when pseudo-first order is preferred, the differences among these two parameters aren't very large. Thus, it seems that the adsorption of 5-FU on carbonaceous materials may be in general better described by the pseudo-second order kinetic model than by the first-order kinetic model. This is in line with Ho and McKay, which analyzed a number of experimental results taken from the literature, and arrived at the conclusion that, for all of the systems studied, the pseudo-second order reaction kinetics provides the best correlation of the experimental data [90].

No clear correlation exists between the pseudo-second order kinetic constant and the initial 5-FU concentration. Despite of this, it is evident that carbon black adsorbents (BP2000 and Vulcan XC72) exhibit much higher constant rates for 5-FU adsorption than the other activated carbons (0.17-0.40 against 0.02-0.06 L^2/g/min/mg). Adsorption kinetics depends on the mesoporous volume, since mesoporous are fundamental for a fast uptake of the pollutant [91]. Analyzing Table 3.4, one can conclude that the obtained results are in line with the textural properties of the used carbonaceous materials. The carbon blacks BP2000 and Vulcan XC72 have much higher mesoporous volume than activated carbons (2.41 and 1.21 against 0.06-0.10 cm^3/g). Figure 3.6 describes the relation between mesopore volume and pseudo-second order kinetic constant: the kinetic of 5-FU uptake increases with the mesopore volume.

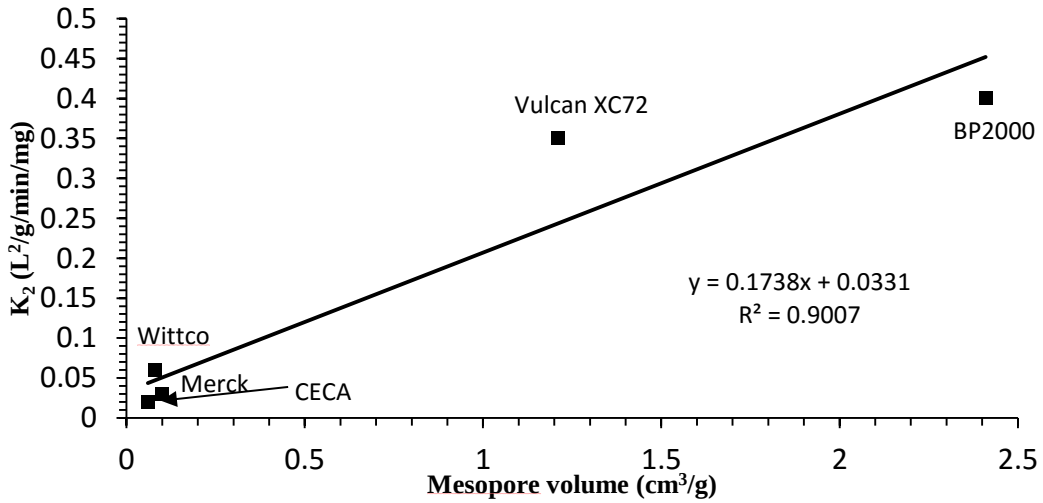


Figure 3.6. Relation between mesopore volume and pseudo-second order kinetic constant.

3.4.1 Influence of agitation and particle size

Agitation and particle size are two factors which influence adsorption kinetic as they affect external and internal mass transfer, respectively. For the study of these two parameters, BP2000 and Norit were chosen, since they have quite distinct textural properties.

Starting by agitation, it influences the distribution/mixing of the solute in the bulk solution, but can also act on the formation of the external boundary film. In a well-agitated batch system, the boundary layer surrounding the particle is much reduced, and in the limit such resistance to mass transfer might be ignored [92]. From the Figure 3.7 is verified that there is no influence of the agitation speed on the 5-FU adsorption process, at least for the conditions tested. Hence, it can be concluded that the external resistance to the mass transfer can be neglected.

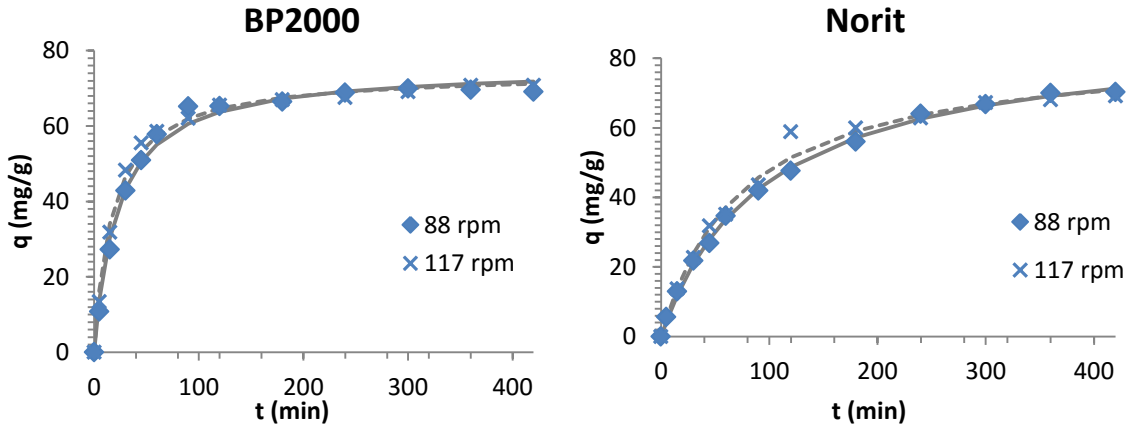


Figure 3.7. Adsorption of 5-FU on BP 2000 and Norit at 88 rpm and 117 rpm ($[5\text{-FU}]_0$ = 10 mg/L, [adsorbent] = 60 mg/L, T = 30.0 ± 0.1 °C, particle size = 212-600 µm). Straight and dashed lines correspond to the pseudo-second order model at 88 and 117 rpm, respectively.

Observing now Figure 3.8 relatively to the study of particle size effect, it is concluded that it influences the sorption rate. When the particle size decreases, the intraparticle diffusion resistance decreases (and also the external surface area of the carbon particles increases). Reducing the particle size resulted in a smaller time to reach the equilibrium. The solute takes less time to diffuse within the particle. The decreased particle size will introduce a lower intraparticle diffusion resistance and will therefore have a higher internal diffusion kinetic coefficient [92].

The curves behavior in Figure 3.8 requires attention: it is verified higher adsorption capacities for carbons with bigger particle size. These results don't correspond with what is expected, since when size is reduced, external surface area increases and more active sites are available for adsorption.

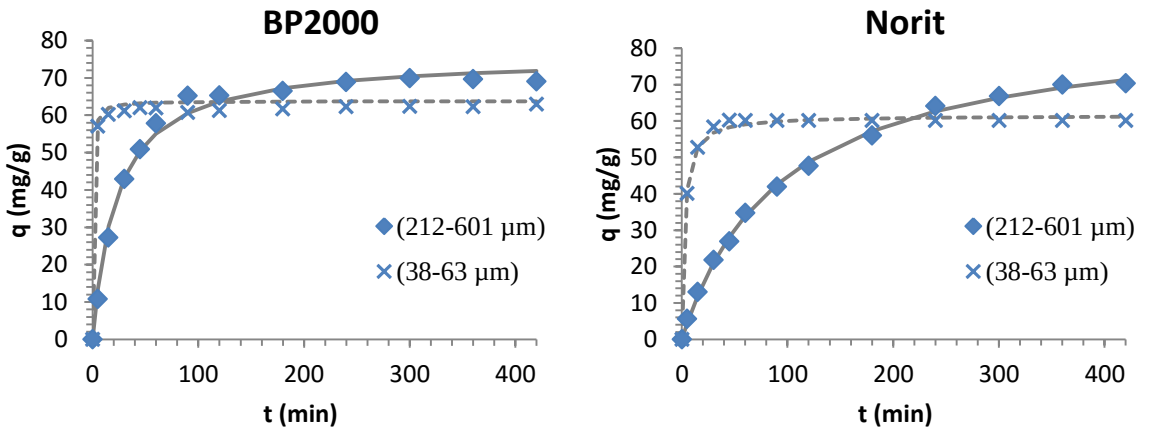


Figure 3.8. Adsorption of 5-FU on BP 2000 and Norit with particle size range = 212-600 µm and 38-63 µm ($[5\text{-FU}]_0$ = 10 mg/L, [adsorbent] = 60 mg/L, T = 30.0 ± 0.1 °C, agitation = 88 rpm). Straight and dashed lines correspond to the pseudo-second order model at 88 and 117 rpm, respectively.

3.4.2 Application of intraparticle diffusion model

To better understand the diffusion mechanism behind the 5-FU adsorption process on carbonaceous materials, the adsorption kinetic data were also analyzed by fitting the intraparticle diffusion model. The Weber-Morris intraparticle diffusion model has been used to describe the adsorption process occurring on a porous adsorbent in a well stirred batch adsorption system [93]. Intraparticle diffusion corresponds to the transfer of adsorbate from the surface to the intraparticular active sites of adsorbent (particle diffusion). Besides this step, there are three more to be considered: the previous transport from the bulk solution to the boundary surface film, from the boundary film to the external surface of the carbon (film diffusion) and the final adsorption of 5-FU on the active sites of adsorbent [94]. In a well stirred batch adsorption system, which is the case, the intraparticle diffusion model has been used to describe the adsorption process occurring on a porous adsorbent [93].

According to this model (Eq.1.3), if the plot of q_t versus $t^{0.5}$ gives a straight line which passes through the origin, then the adsorption process is only controlled by intraparticle diffusion, whereas, if the data exhibit multilinear plots, then two or more steps (resistances) inside the particles influence the adsorption process. Moreover, if there is a deviation of the straight line from the origin, this means that intraparticle transport is not the only rate limiting step [92]. The deviation of plots from the origin may be due to the difference between the rate of mass transfer in the initial and final stages of adsorption [95]. The results obtained from the fit of Weber-Morris intraparticle diffusion model to the experimental data are shown in (Figure 3.9 and Table 3.8).

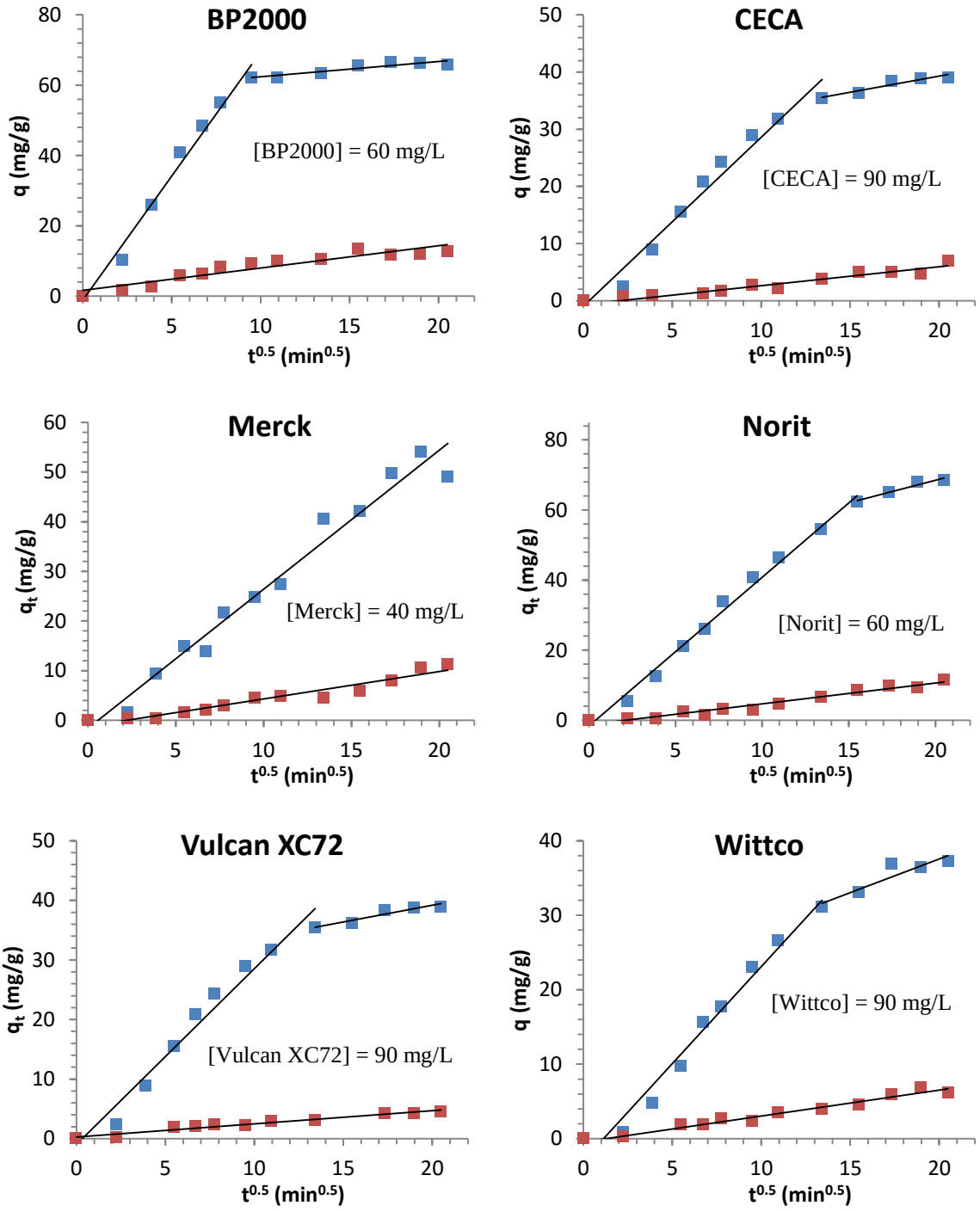


Figure 3.9. Morris and Weber linear plot for adsorption of 5-FU on BP 2000, CECA, Merck, Norit, Vulcan XC72 and Wittco (5-FU initial concentration of 1 mg/L and 10 mg/L (T = 30.0 ± 0.1 °C, agitation = 88 rpm, particle size = 212-600 µm). Red and blue dots correspond to the fitted models for 1.0 and 10 mg/L, respectively.

All carbons, with the exception of Merck, present multilinearity for the 5-FU initial concentration of 10 mg/L. The initial steep phase may represent macropore and mesopore diffusion and the second steep phase, the micropore diffusion. The larger slopes of the first sharp sections

indicate that the rate of 5-FU diffusion is higher in the beginning stage. The lower slopes of the second sharp portion are due to the lower 5-FU concentration gradients within the pores and the consequent lower diffusion rates, as observed also in other studies [94] [96]. It is assumed that the external resistance to mass transfer surrounding the particles can only occurs (not necessarily) in the early stages of adsorption, represented by the first sharper portion [96].

Table 3.8. Intraparticle diffusion model parameters for adsorption of 5-FU on carbonaceous materials (T = 30.0 ± 0.1 °C, agitation = 88 rpm, particle size = 212-600 µm).

Adsorbent material	$[5\text{-FU}]_0$ (mg/L)	Intraparticle diffusion model					
		First steep phase			Second steep phase		
		k_{d1} (mg/(g.min$^{1/2}$))	I_1 (mg/g)	R_1^2	k_{d2} (mg/(g.min$^{1/2}$))	I_2 (mg/g)	R_2^2
BP2000	1.0	0.64	1.67	0.89	-	-	-
(60 mg/L)	10	7.06	-1.11	0.98	0.44	57.98	0.84
CECA	1.0	0.33	-0.70	0.88	-	-	-
(90 mg/L)	10	2.96	-0.97	0.97	0.56	28.06	0.91
Merck	1.0	0.55	-1.24	0.94	-	-	-
(40 mg/L)	10	2.80	-1.58	0.97	-	-	-
Norit	1.0	0.60	-1.28	0.96	-	-	-
(60 mg/L)	10	4.25	-1.68	0.99	1.29	42.65	0.94
Vulcan XC72	1.0	0.22	0.28	0.96	-	-	-
(90 mg/L)	10	2.95	-0.96	0.97	0.56	27.98	0.91
Wittco	1.0	0.35	-0.45	0.95	-	-	-
(90 mg/L)	10	2.60	-2.95	0.98	0.90	19.52	0.86

For all materials studied, the constant I (mg/g) obtained for the first steep phase is within the range of uncertainty associated to the origin. This suggests that the thickness of the boundary layer is very small and consequently the mass transfer resistance within the film could be neglected. This point is in agreement with the results obtained in the last section for BP2000 and Norit, when the effect of different agitation speeds on the adsorption kinetic was studied. It is observed a favourable dependence of the adsorption rate constant with the increase of the initial 5-FU concentration is noticed; higher intraparticle diffusion rate constant, k_d, were obtained for the highest 5-FU concentration.

3.5 Adsorption isotherms

The adsorption isotherms of 5-FU on carbonaceous materials were obtained by plotting the amount of 5-FU adsorbed in the solid phase against the 5-FU concentration in the liquid phase, both under equilibrium conditions (i.e., after 24 h of contact between the sold and the liquid phase). Langmuir, Freundlich, Sips and Temkin isotherm models (respectively equations Eq.1.10, Eq.1.11, Eq.1.13 and Eq.1.12) were considered to describe the experimental results. The parameters of the

isotherms were determined by fitting the models to the experimental data through non-linear regression. The results obtained are compiled in Table 3.9 and shown in Figure 3.10.

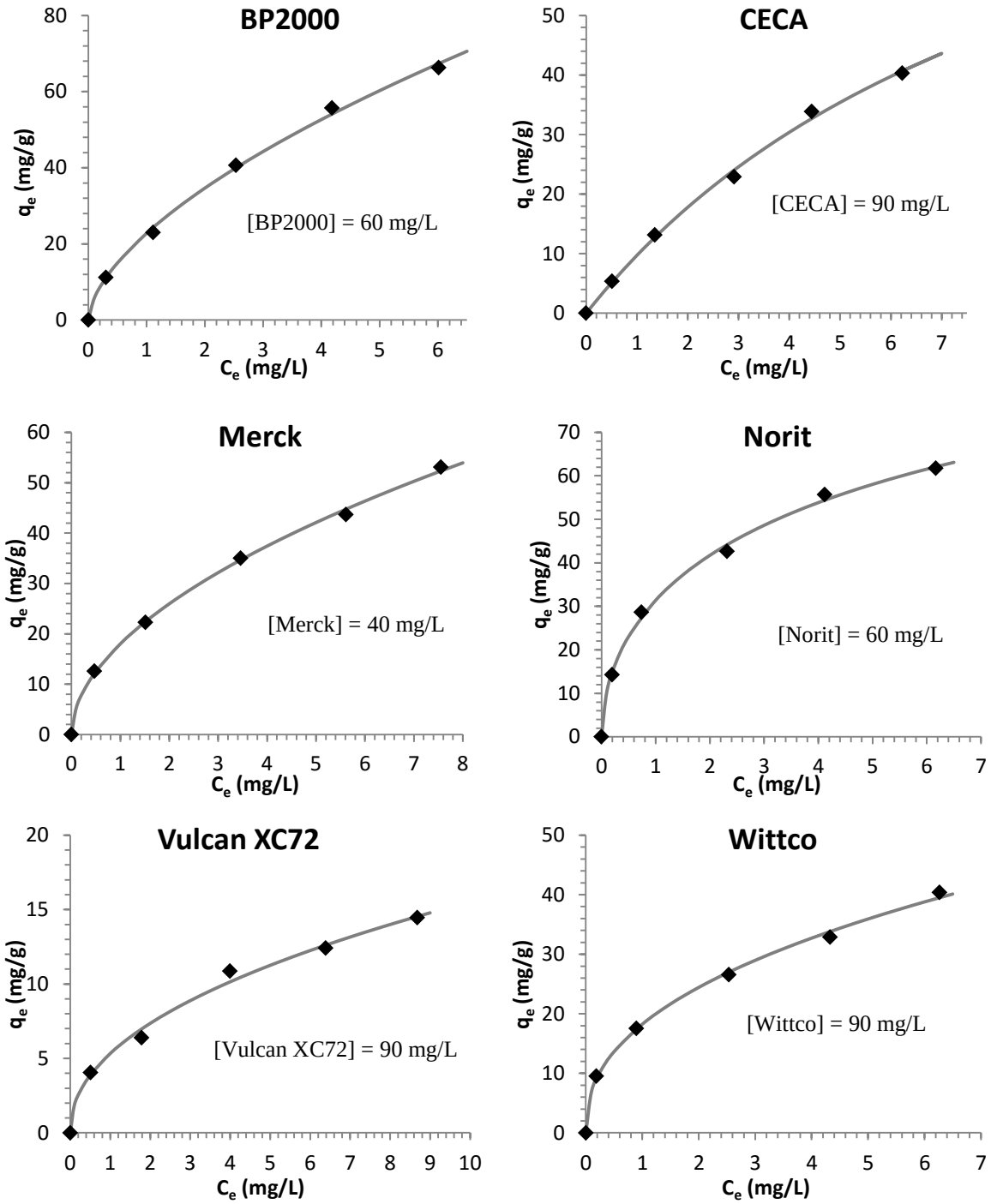


Figure 3.10. Adsorption isotherms for 5-FU on BP2000, CECA, Merck, Norit, Vulcan XC72 and Wittco for a 5-FU initial concentration of 1.0 – 10 mg/L (T = 30.0 ± 0.1 °C, agitation = 88 rpm, particle size range = 212-600 µm, contact time =24 h). In each graph is represented the best fitted model according with Table 3.9.

Table 3.9. Parameters of adsorption isotherms for 5-FU on carbonaceous materials (T = 30.0 ± 0.1 ºC, agitation = 88 rpm, particle size = 212-600 µm). In bold are highlighted the best model for each situation.

Adsorbent material		BP2000 (60 mg/L)	CECA (90 mg/L)	Merck (40 mg/L)	Norit (60 mg/L)	Vulcan XC72 (90 mg/L)	Wittco (90 mg/L)
Langmuir isotherm	q_L (mg/g)	111.99	104.02	74.39	70.23	18.68	46.63
	K_L (L/mg)	0.24	0.10	0.28	0.89	0.34	0.66
	MSC	5.54	**6.43**	6.29	4.63	7.33	3.96
Freundlich isotherm	K_F (mg/g)	22.80	10.37	18.01	30.75	5.33	18.25
	n_F	1.66	1.32	1.90	2.53	2.16	2.38
	MSC	**6.53**	5.85	**8.86**	4.63	**8.31**	**6.78**
Sips isotherm	q_S (mg/g)	280.84	109.60	267761.33	144.10	75.66	68673.24
	n_S	1.41	1.02	2.16	1.82	1.89	2.38
	K_S	0.09	0.10	0.00	0.28	0.08	0.00
	MSC	6.37	5.90	5.99	**6.13**	7.81	6.25
Temkin isotherm	K_T (L/mg)	4.60	2.34	4.12	12.38	4.67	12.93
	b (J.g/mg/mol)	137.05	180.35	177.67	182.98	681.42	302.37
	MSC	3.34	3.66	5.55	4.95	6.89	3.92

It is verified that there isn't a total accordance between the carbons and the best model. While the adsorption of 5-FU on BP2000, Merck, Vulcan XC72 and Wittco is better described by Freundlich model, the adsorption on CECA is better fitted by Langmuir and Norit by Sips. For these three models, the values of MSC are not very different among them, whereby they were all study in order to a better comprehension of the adsorption isotherms.

When the parameter n_S of the Sips model (Eq.1.13) is lower than the unit, it indicates some degree of heterogeneity in terms of active sites for 5-FU uptake, as Freundlich model proposes [97]. Alternatively, when n_S is equal to 1, this equation becomes a Langmuir equation [98]. The q_S values suggest a higher adsorption capacity for BP2000 followed by Norit, CECA and Vulcan XC72, which is in agreement with their surface area. The other two adsorbents, Merck and Wittco, have adsorption capacities overly high comparing to the others, whereby they weren't considered for analyze by Sips model.

The same analysis can be made for q_L of Langmuir model (Eq.1.10), which describes quantitatively the formation of a monolayer adsorbate on the surface of the adsorbent [99]. Observing Figure 3.11 which relates surface area with q_L is verified a tendency: an increase of surface area allows a higher uptake of 5-FU. The deviations from this behavior may result from surface chemistry influence.

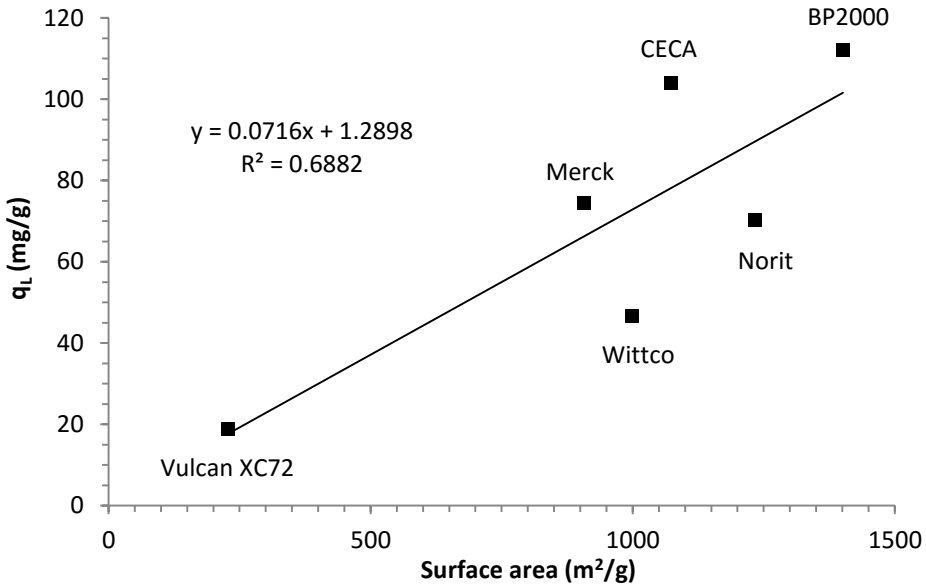


Figure 3.11. Relation between surface area and adsorption capacity.

The values of n_F in the Freundlich model (Eq.1.11) are higher than unity for all carbons, indicating that higher energies are involved in the adsorption of 5-FU molecules on the materials surface. This may suggest that slight chemical interactions may be stablished during the adsorption process; although, as explained in the introduction section, it is very difficult to distinguish between physical and chemical adsorption due to the large range of binding energies associated to each other [46]. However, the bad description of the experimental results by the Temkin isotherm (Eq.1.13), which is well-known to give evidences of chemisorption [100], may indicate that the high bond energies may be associated to physical interactions between 5-FU and carbonaceous. The constant K_F is an approximate indicator of adsorption capacity [99], however a relation among their values and surface area is not possible to be stablished.

4 Conclusions

Cytostatic drugs are substances widely used in the treatment of cancer; among them the most commonly consumed is 5-FU. Even at low concentrations, 5-FU has potential carcinogenic, mutagenic, genotoxic, cytotoxic and teratogenic effects. Since none of the conventional processes allow an efficient removal of 5-FU, a new methodology should be developed (e.g. adsorption + AOPs). The focus of this work was the first step of this new approach: the concentration of the effluent by adsorption to be posteriorly degraded by AOPs. To perform the adsorption of 5-FU, activated carbons, carbon blacks and zeolites were tested.

Based on the information described in the literature, activated carbons and MIPs have been found to have adsorption capacities towards 5-FU in the range of 0.38 – 0.86 mg/g and 0.35 – 0.65 mg/g, respectively. Other materials were studied relatively to adsorption of 5-FU, but for drug controlled realize purposes.

Zeolites tested in this work have demonstrated a poor capacity to remove 5-FU, even in extreme conditions, whereby they were discarded from this study. Adsorption over carbon-based materials was far more significant, with adsorption capacities in the range of 18.68 and 111.99 mg/g, according with Langmuir model.

The pseudo-second order kinetic model gave the best fit to the kinetic results. Carbon blacks (BP2000 and Vulcan XC72) present faster 5-FU adsorption than activated carbons. These results showed a correlation between the carbon mesoporosity and the kinetics of adsorption: higher mesoporosity allows a faster uptake of 5-FU, in other words, higher k_2 values.

The influence of the agitation speed and particle size on the 5-FU adsorption was studied for some carbonaceous materials, namely BP2000 and Norit. It was verified that the agitation speed has no effect on the 5-FU adsorption process, at least for the conditions tested. Therefore, external resistance to the mass transfer can be neglected. By applying intraparticle diffusion model, similar conclusions were achieved: the diffusion inside the pores seemed to be the rate-controlling mechanism, whereby film diffusion has none influence in the process. Regarding the particle size, it was observed that the uptake of 5-FU is faster for smaller particles. This could be explained by the decrease of the intraparticle diffusion resistance and the increase of the external surface of the carbon particles when the particle size is decreased.

By the study of isotherms, it was possible to conclude that there isn't a model which describes all the materials. While the adsorption of 5-FU on BP2000, Merck, Vulcan XC72 and Wittco is better described by Freundlich model, the adsorption on CECA is better fitted by

Langmuir and Norit by Sips. Comparing adsorption capacity with surface area, there is a tendency of major uptakes of 5-FU for higher surface areas; although without a good linearity among both, which may be explained by the influence of the chemical surface.

5 Limitations and suggestions for future work

Although good results were achieved and the main objectives of this work were met, there were some limitations, most of them associated with time and the availability of the equipments used.

Initially it was found that there isn't much information in the literature about the 5-FU removal by adsorption (related to the novelty of this thematic), which led to the necessity to carry out some preliminary tests related with the adsorbents and adsorbate concentrations to be able to perform the kinetic and isotherm studies.

This work was the first step of a methodology which aims to degrade 5-FU after its removal by adsorption. The adsorption results were interesting, whereby they should be used to complete this method and to achieve an efficient process to remove 5-FU from waters. As future work, the author would like to suggest:

- To use other analytical method, which allows to analyze lower concentrations, more close to those present in real water systems;
- To study other parameters influencing the adsorption kinetics, as pH and temperature;
- To study the process in a real effluent in order to evaluate its efficiency in the presence of other compounds;
- To perform elemental more detailed characterization analysis of the adsorbent materials tested to understand how surface chemistry influences adsorption performance;
- To perform 5-FU degradation by Fenton reaction after its adsorption/concentration on a given adsorbent. Two approaches could be performed: the reaction inside the adsorbent or pre-elution of the pollutant followed by its degradation in the liquid phase (outside the adsorbent).

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Appendix A – Other adsorbents

A.1 Molecular imprinted polymers

Molecular imprinted polymers (MIPs) are molecular recognition materials able to mimic natural recognition entities, providing highly selective and affinity polymer receptors for given molecules, their analogues or for a single enantiomer [101] [51]. They are capable to recognize both biological and chemical molecules, where are included amino acids, proteins, nucleotide derivatives, pollutants, drugs and food. They are recognized by non-covalent interactions, such as hydrogen and hydrophobic bonding, and are influenced by the nature of the template and monomers, which determine the quality and performance of the polymer product. The ability to selectively recognize a target molecule in a pool of similar molecules is essential for biological and chemical processes [51] [102] [103]. MIPs are easy to prepare, inexpensive, have high mechanical strength, durability to heat and pressure, good thermal and chemical stability and can be reused without loss of activity [101]. Presently, they are used in several processes as separation, pre-concentration, constructing sensors, chromatography, among others [104].

A.2 Fibers

The definition of fibers is not easy to be given, since is a very embracing term, being characterized as material with the following properties:

- High length/diameter ratio (at least 1000);
- High flexibility;
- Small diameter (10 to 200 μm);
- Cohesion;
- Tenacity;
- Uniformity of properties.

The two main divisions in fibers are natural and manufactured: natural fibers are those found in nature and the two main sources are plants and animals. Manufactured fibers are formed from a suitable raw material as a thick, sticky liquid, which is “spun” or extruded through spinneret holes, forming streams that are solidified into fibers [105]. Electrospinning is one of the most used methods to fabricate fibers with small diameters, which is highly dependent upon the conductivity of the spinning solution [106].

A.3 Graphene

Graphene corresponds to a flat monolayer of carbon atoms tightly packed into a two-dimensional (2D) honeycomb lattice with a carbon-carbon distance of 0.142 nm, and is a basic building block for graphitic materials of all other dimensionalities. Graphene has a number of remarkable mechanical and electrical properties, being substantially stronger than steel and very stretchable. The thermal and electrical conductivity is very high and it can be used as a flexible conductor [107]. In addition, it has excellent biocompatibility and low toxicity properties [108].

Graphene was never used for 5-FU removal, but medical experimental were already performed, where 5-FU was loaded into it. Wei and co-workers described a process where a nanocomposite of Fe_3O_4 and graphene oxide (GO) was used firstly for loading of 5-FU and then its controlled release. This composite has two functions: integration of magnetic resonance imaging (MRI) characteristics to control drug delivery performed by Fe_3O_4, which is not relevant for this study, and adsorption of 5-FU by graphene oxide [108]. To calculate the loading capacity of Fe_3O_4/GO nanocomposites, ultraviolet visible spectroscopy was performed.

A.4 Experimental results

Abraham et al. (2014) studied the ability of MIPs to adsorb 5-FU. The objective of this work was to open new horizons in the design of new artificial receptors. The main characteristics of two MIPs are presented in Table A.1. It is important to notice that they were obtained from the same polymerization mixture (i.e., the same template, functional monomers, cross-linker, initiator, porogenic solvent and extraction solvent), but by different polymerization methodologies. One was synthesized by traditional bulk imprinting method and the other was obtained by reversible addition fragmentation chain transfer polymerization on the surface of functionalized multiwalled carbon nanotubes (MWCNTs) (Table A.2). The only operating condition mentioned by the authors was the 5-FU initial concentration.

Table A.1. Characteristics of MIPs and 5-FU initial concentration used to treat water contaminated with 5-FU [104].

Adsorbent	Template	Functional monomer	Cross-linker	Initiator	Porogenic solvent	Extraction solvente	$[5FU]_0$ (mg/L)
MIP	5-FU	MAA[a]	EGDMA[b]	AIBN[c]	Mixture of acetonitrile and toluene	Methanol	0.22
MIP grafted on MWCNT							

Notes: [a] Methacrylic acid; [b] Ethylene dimethacrylate; [c] 2, 2' azoisobutyronitrile.

Table A.2. Characteristics of MWCNT used to support MIPs [104].

Internal diameter (nm)	Outer diameter (nm)	Length (nm)	Purity (%)
2-6	10-15	0.1-10	> 90

As observed for zeolites, fibers were only investigated as adsorbents of 5-FU for control drug delivery purposes (Table A.3). As happen in zeolites, the concentration of 5-FU involved in the experiments is very high compared to the values found in water systems. The temperatures don't correspond, as well, to real values. The concentrations of adsorbent were not defined by the authors. Both fibers were produced by electrospinning method.

Table A.3 Characteristics and operating conditions of the fibers used to loading and realize of 5-FU [109] [106].

Adsorbent	Molecules	Fiber fabrication method	Fiber diameter (μm)	Matrix	$[5\text{-FU}]_0$ (mg/L)	T (^{0}C)	pH
PLA fiber	poly(lactic acid)	Electrospinning	28	water	15000	70-110	8
Starch Acetate fiber	Starch acetate	Electrospinning	50		1.4×10^4	70-90	7

In terms of characterization of graphene, there isn't information available, whereby Table A.4 will be only about the operating conditions. As some of the previously cases, the aim to the graphene experience is to load and release 5-FU in human body, thereby the concentration of 5-FU is very high and the matrix is PBS solution, in order to mimic the human condition, which is not in agreement with what happen in water systems.

Table A.4. Operatory conditions for Fe_3O_4/graphene oxide nanocomposites [108].

Adsorbent	Matrix	[adsorbent] (mg/L)	$[5\text{-FU}]_0$ (mg/L)	Temperatute (^{0}C)	pH
Fe_3O_4/graphene oxide nanocomposites	PBS [a]	250	500	20	7,4

Notes: [a] Phosphate-buffered saline

Observing Table A.5, which contain the adsorption results, it is clearly the difference between the adsorption capacities of adsorbents used for cleaning purposes (MIPs) and the adsorbents used for health care (fibers and graphene). The operating conditions used maybe are the reason of such difference.

The MIP produced by traditional bulk imprinting method presents lower adsorption capacity than the other (Table A.1). The higher adsorption capacity for MIP grafted on MWCNTs is due to the higher accessibility to the specific sites, which allow a faster mass transfer and binding kinetics

[104].The MWCNTs, or merely graphene, has itself characteristics that make it able to adsorb 5-FU on its surface, which can influence the adsorption capacity as well. Comparing the adsorption studies of MIPs with the ones performed with activated carbon, it can be concluded that MIPs exhibit similar adsorption capacities, even for the treatment of waters with very low contamination charges (5-FU concentrations of 0.22 mg/L for MIP against 0.1 mg/L for activated carbon).

The experimental results for fibers were performed under a range of temperatures, whereby the results of adsorption capacity vary. The increase of temperature will raise the 5-FU adsorption into fibers, since the diffusion coefficient will be higher [109].

The results for graphene were very similar to the zeolites and fiber results. For these adsorbents, the experimental conditions were completely different from the desire, with especially focus to the 5-FU initial concentration, which may is the responsible for such high values of adsorption capacity.

Table A.5. Adsorption properties of some adsorbents [104] [108] [109] [106].

Adsorbent		**Equilibrium time (min)**	**Adsorption capacity (mg/g)**	**Kinetic model**	**Isotherm model**
MIP	MIP	120	0.35	-	Langmuir
	MIP grafted on multiwalled Carbon nanotubes	120	0.65	Pseudo-second order	-
Fiber	PLA fiber	150	0.6 – 1.3	-	Langmuir
	Starch Acetate fiber	90	8.9 – 9.6		
Graphene	Fe_3O_4/graphene oxide nanocomposites	-	370	-	-

Appendix B – Regeneration of activated carbon

Regeneration offers clear advantages, such as a lower consumption of activated carbon and the possibility of recovering adsorbed products of potential economic value. Besides that, its regeneration implies costs that on some occasions are not much lower than the cost of the production of new activated carbon and provides activated carbon with lower adsorption capacity than the original, since it leads to heavy losses of carbon. Taking into account these considerations, this procedure is almost exclusively viable with granular activated carbon [53]

Regeneration of carbon has been conducted in varied different ways:

- Thermal regeneration;
- Steam regeneration;
- Regeneration with solvents;
- Supercritical fluid regeneration;
- Chemical regeneration;
- Biological regeneration.

Regeneration can be explained as combination of desorption and activation, in other words, a first phase where the contaminants are removed from the carbon and a second phase with the destruction of contaminants [110]. Regeneration and reactivation are often used interchangeably, although the term regeneration refers to the process of removing the adsorbed contaminant from activated carbon and reactivation to the process of removing the adsorbed contaminant. This happen, because regeneration, by itself, is usually ineffective at restoring the adsorption capacity of the carbon [111].

Appendix C – Properties of zeolites

Table C.1. Properties of zeolites [82].

Name	SiO_2/Al_2O_3 Mole Ratio	Nominal Cation Form	Specific surface area (m^2/g)	Supplier
CZB 25	25	Hydrogen	> 500	Clariant
CP814C	38	Ammonium	710	Zeolyst
CZM 20	20	Ammonium	> 400	Clariant
P-38	38	Hydrogen	>380	ACS Materials
CZP 90	80-100	Hydrogen	> 299	Clariant
CZP 30	25-30	Hydrogen	> 300	Clariant